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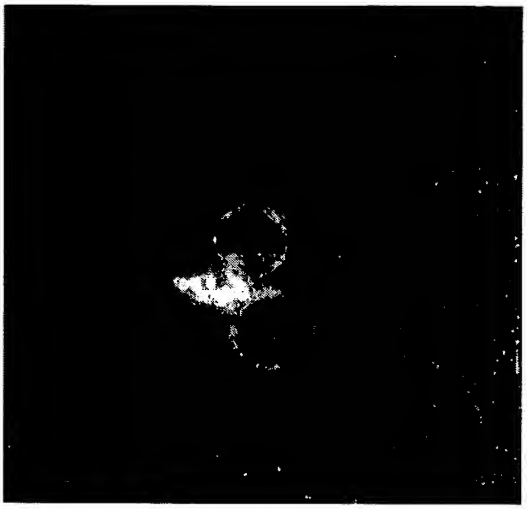
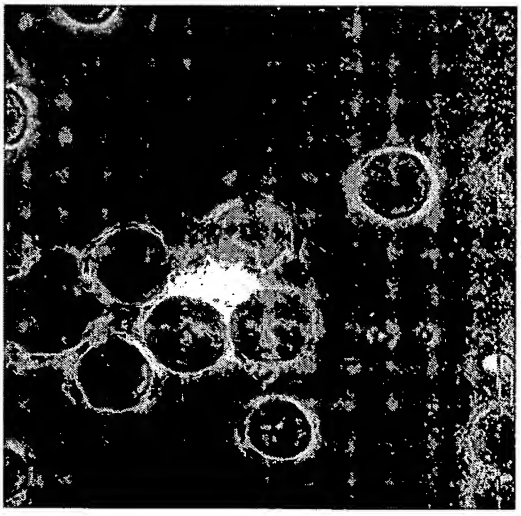
Figure 1

Fusion of Cochleate Membrane with Target Cells



Fluorescent Image



Phase/Fluorescent Image

Figure 2

Formulation of Hydrophobic Cargo Moiety Into Cochleates: Solvent Drip Method

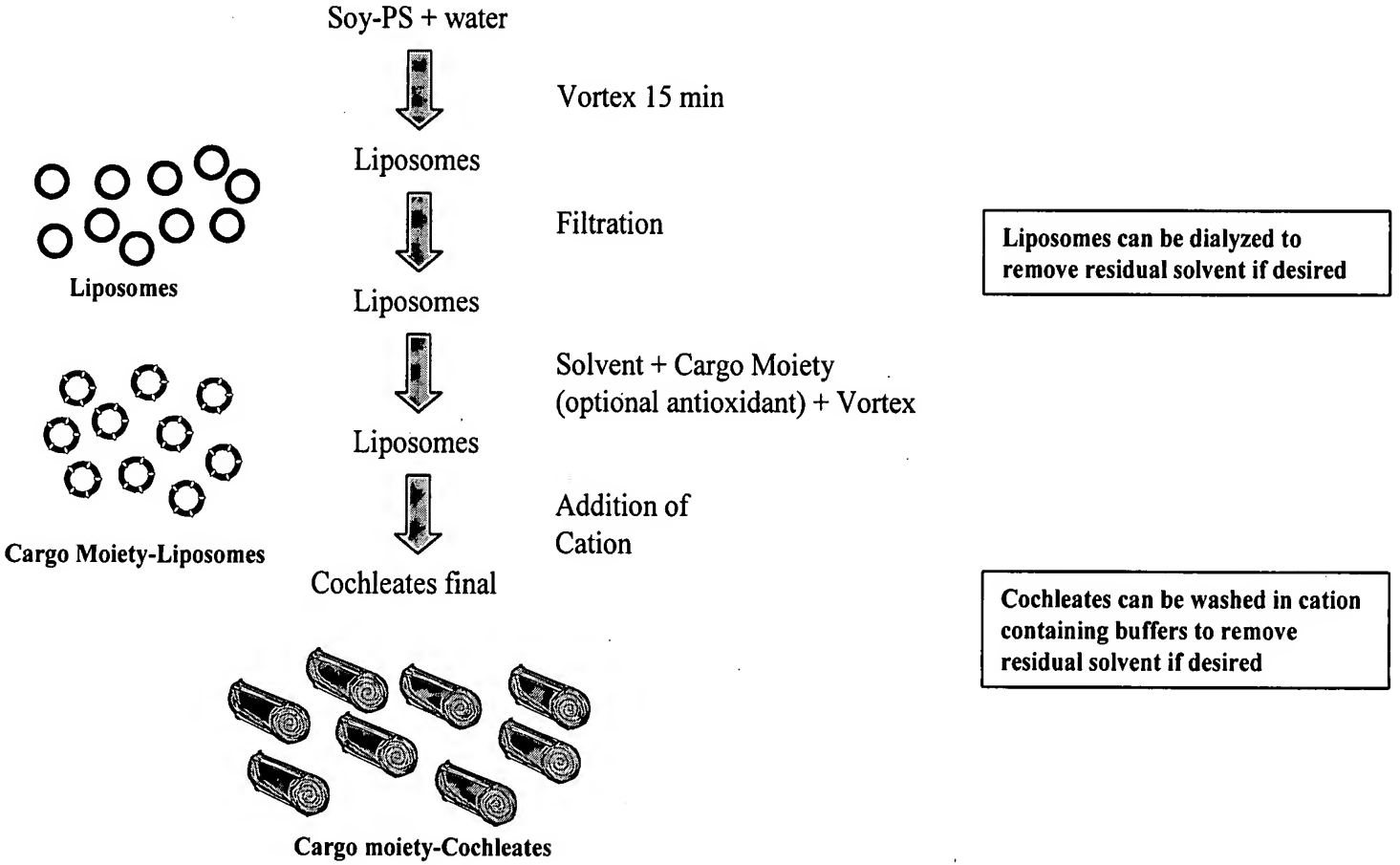


Figure 3

Formulation of Hydrosoluble Cargo Moieties Into Cochleates:
Trapping method with preformed liposome

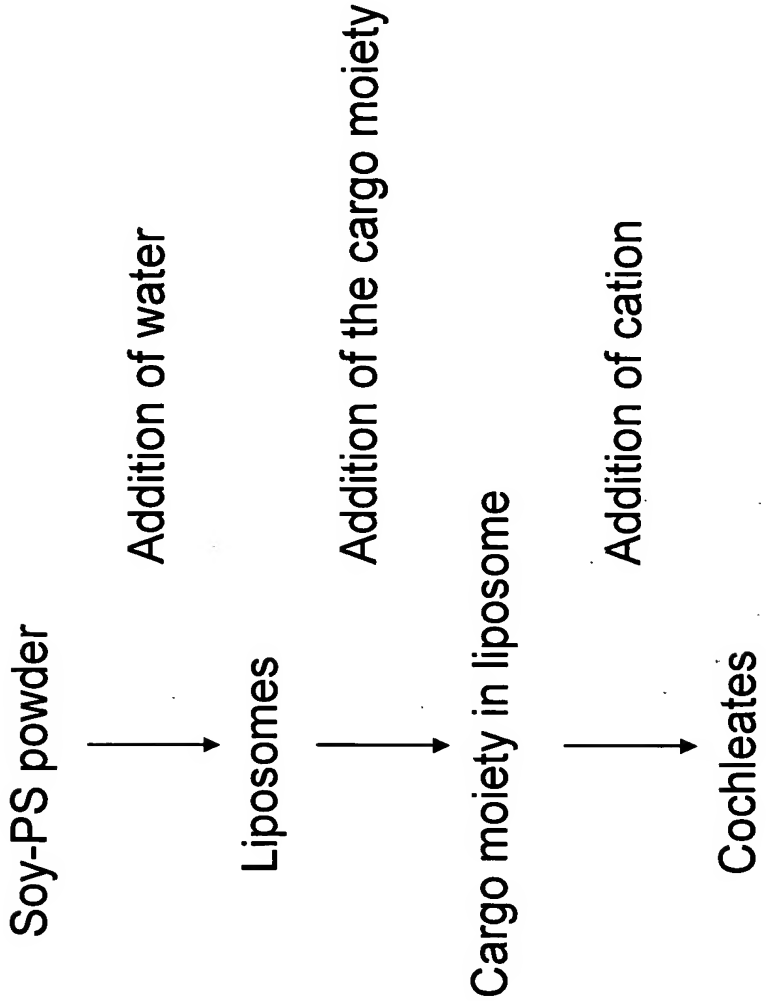


Figure 4

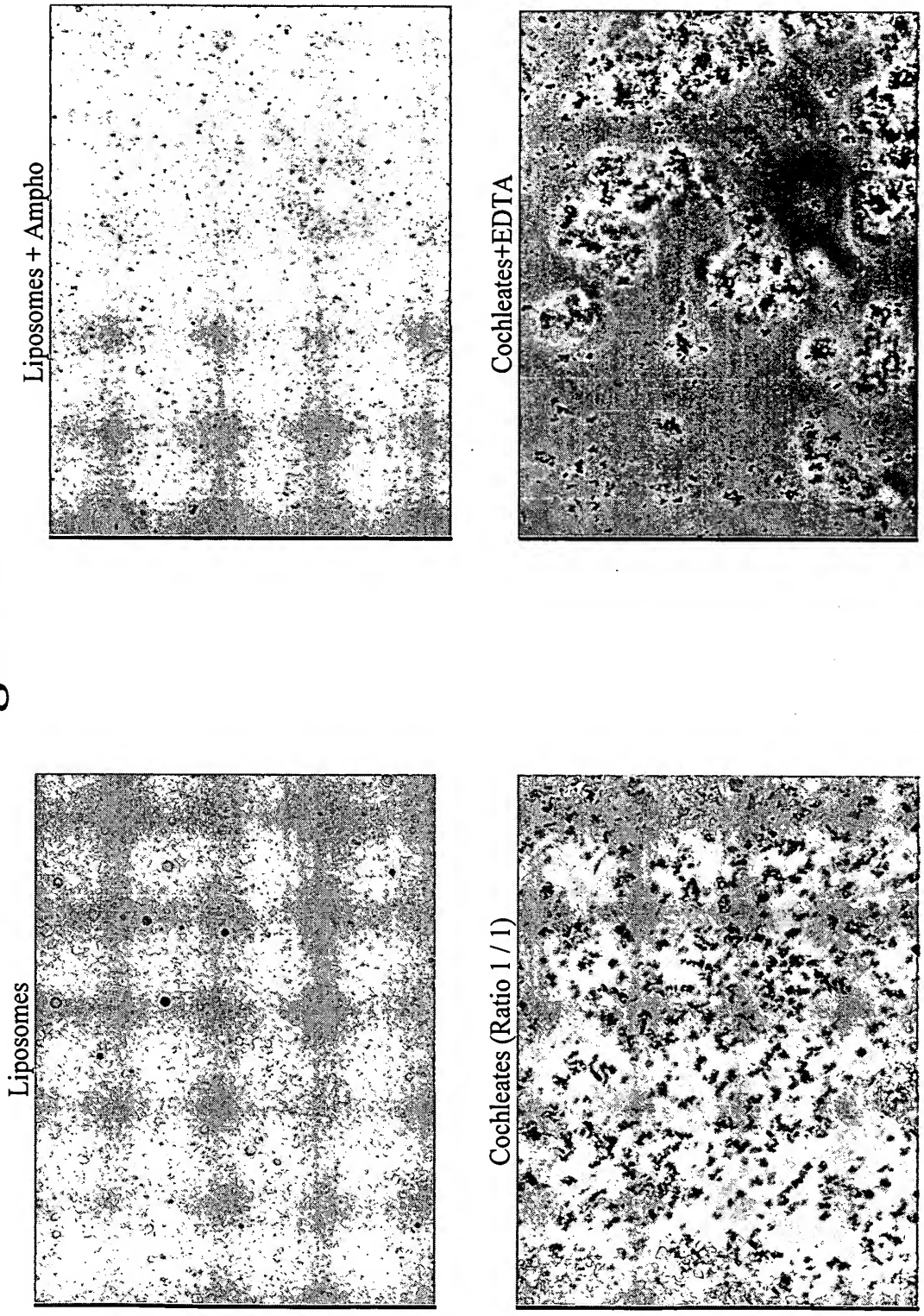

Liposomes + Ampho
Cochleates+EDTA
Liposomes
Cochleates (Ratio 1 / 1)

Figure 5

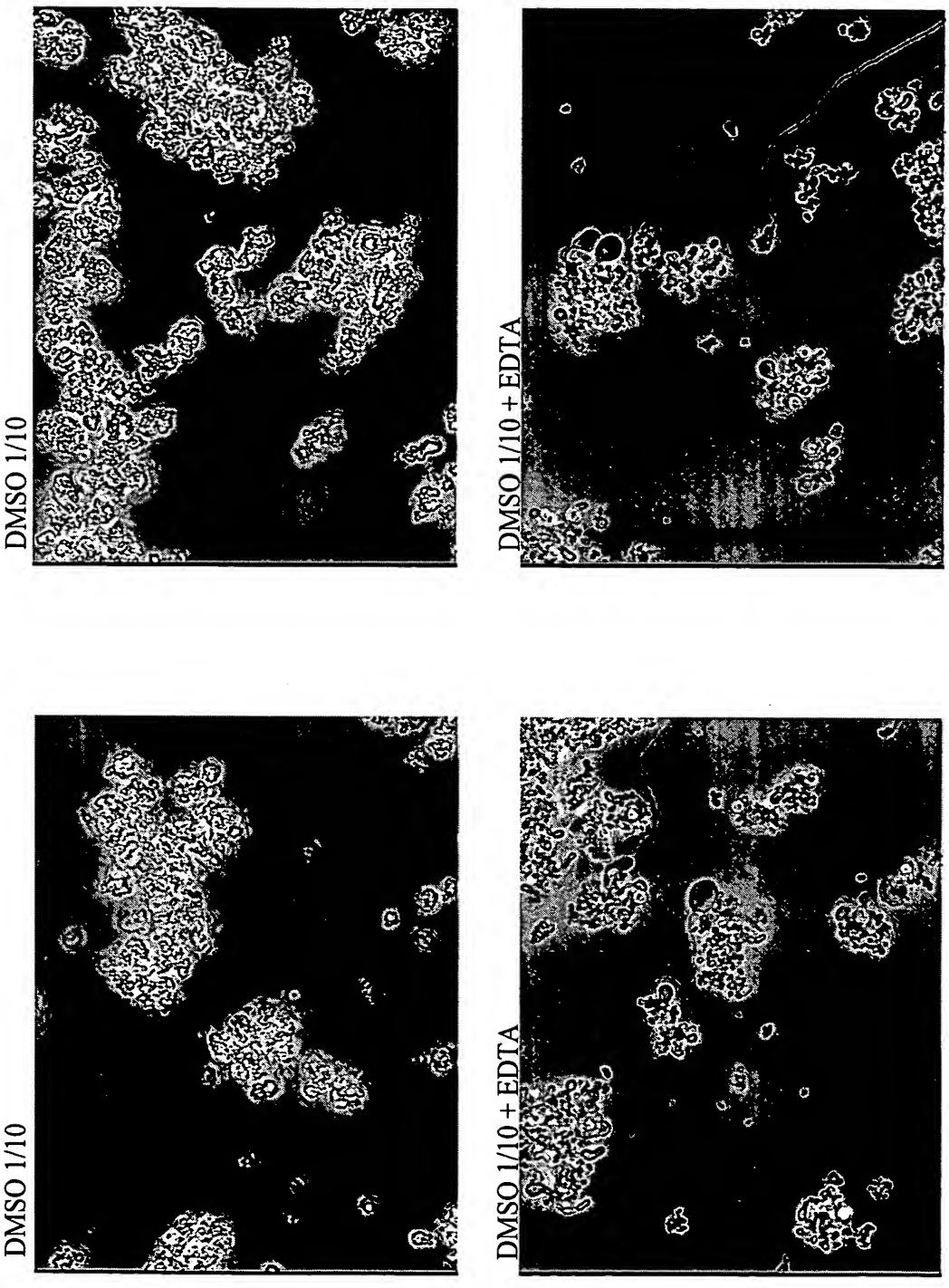


Figure 6

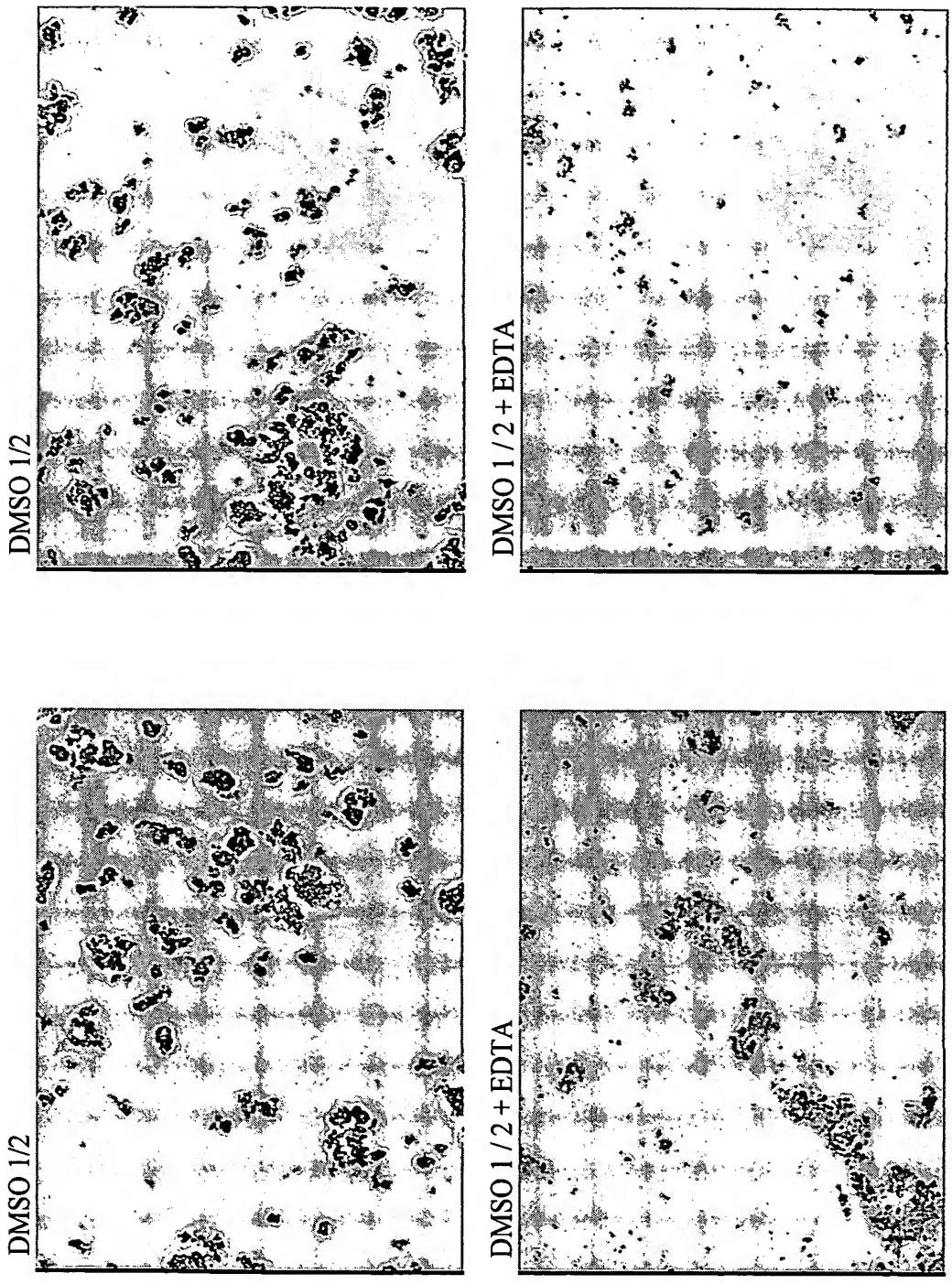
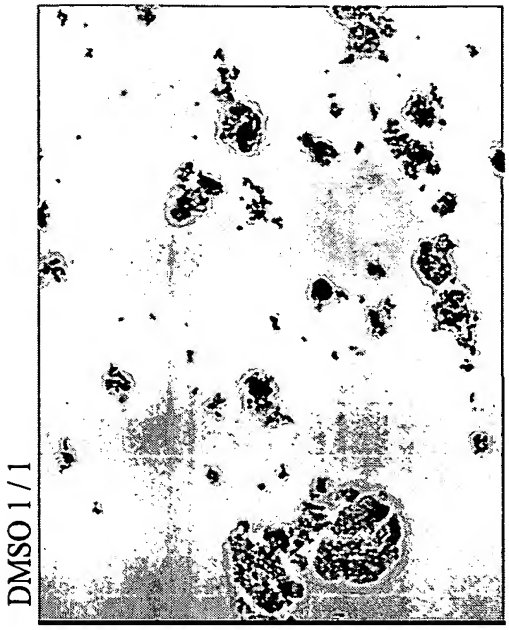


Figure 7



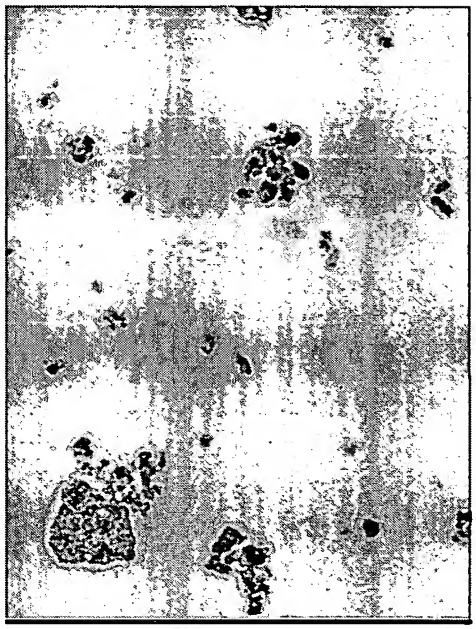


Figure 8

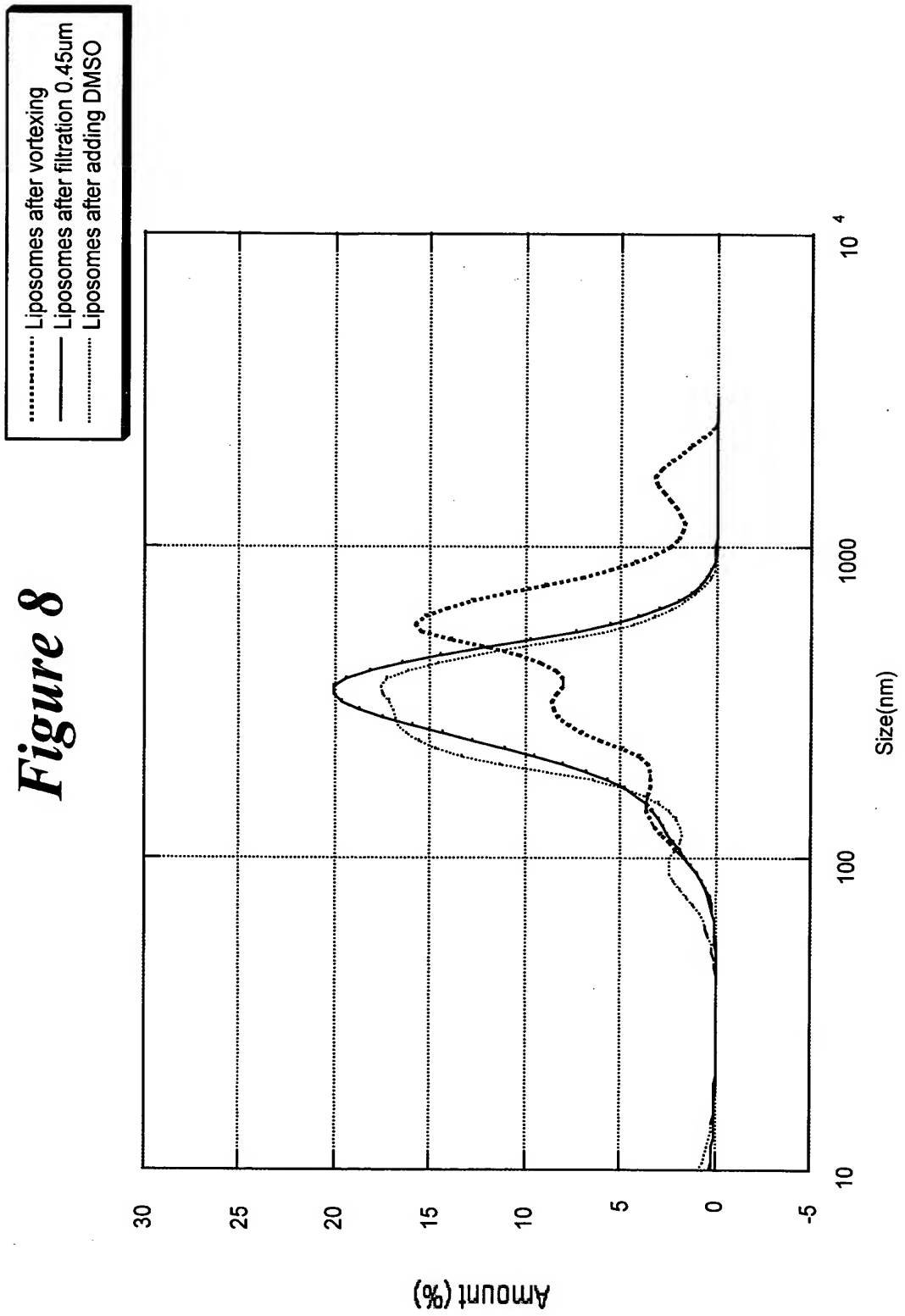

Liposomes after vortexing
Liposomes after filtration 0.45um
Liposomes after adding DMSO
Amount (%)
30
25
20
15
10
5
0
-5
10
100
1000
10 4
Size(nm)

Figure 9

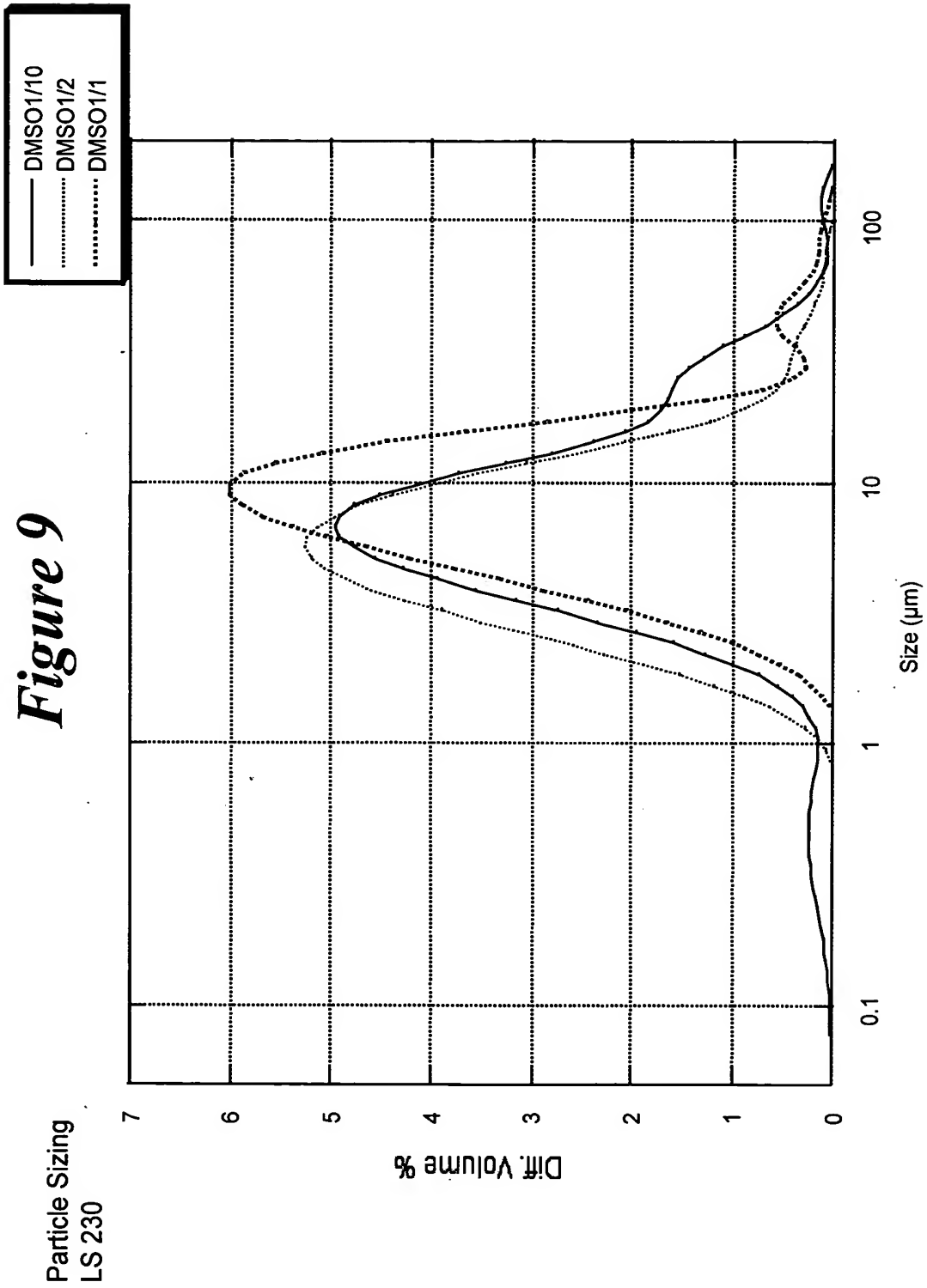

DMSO1/10
DMSO1/2
DMSO1/1
Diff. Volume %
0
1
2
3
4
5
6
7
0.1
1
10
100
Size (µm)
Particle Sizing
LS 230

Figure 10

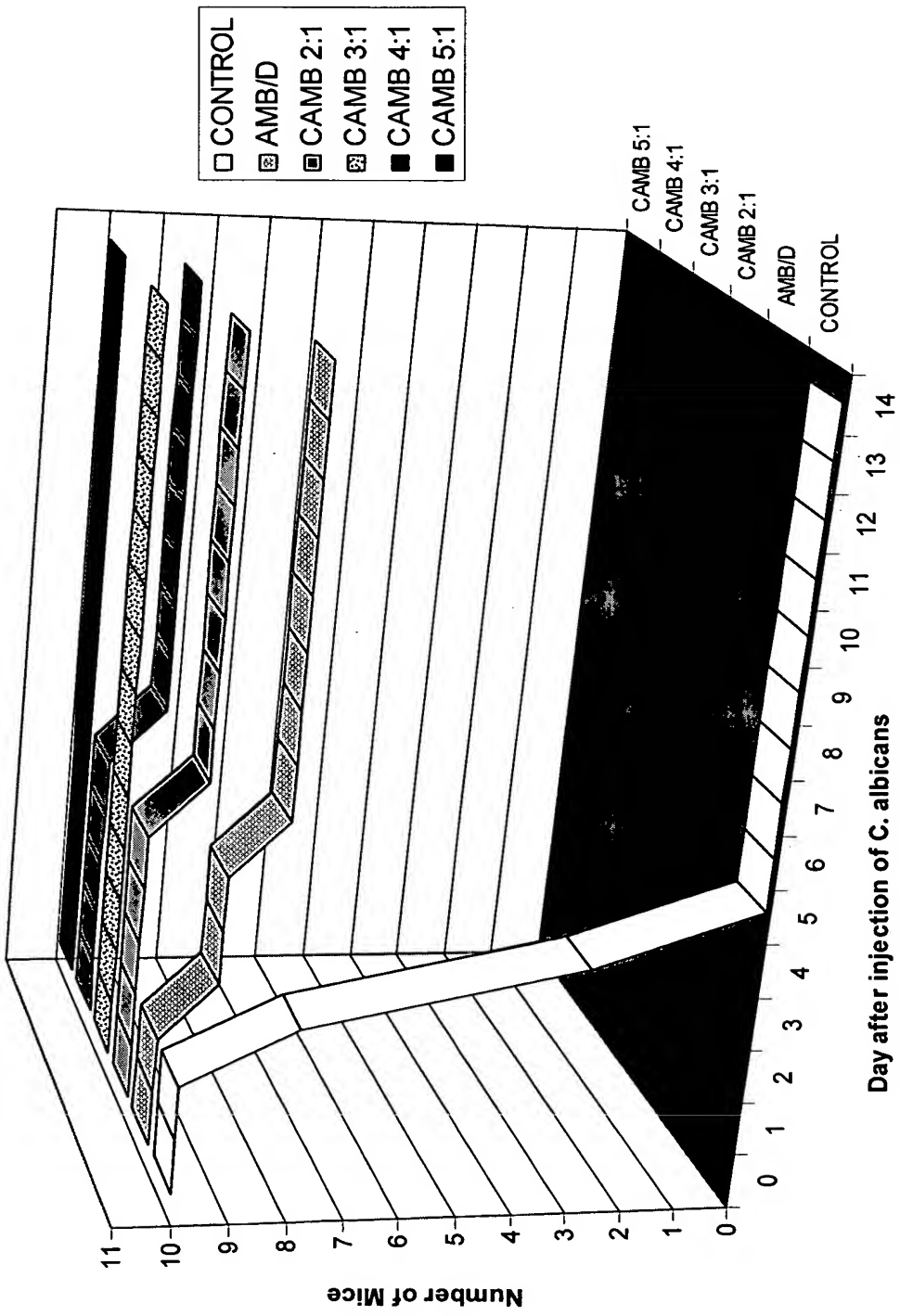

Survival Data
CONTROL
AMB/D
CAMB 2:1
CAMB 3:1
CAMB 4:1
CAMB 5:1
Number of Mice
0
1
2
3
4
5
6
7
8
9
10
11
Day after injection of C. albicans
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
CONTROL
AMB/D
CAMB 2:1
CAMB 3:1
CAMB 4:1
CAMB 5:1

Figure 11

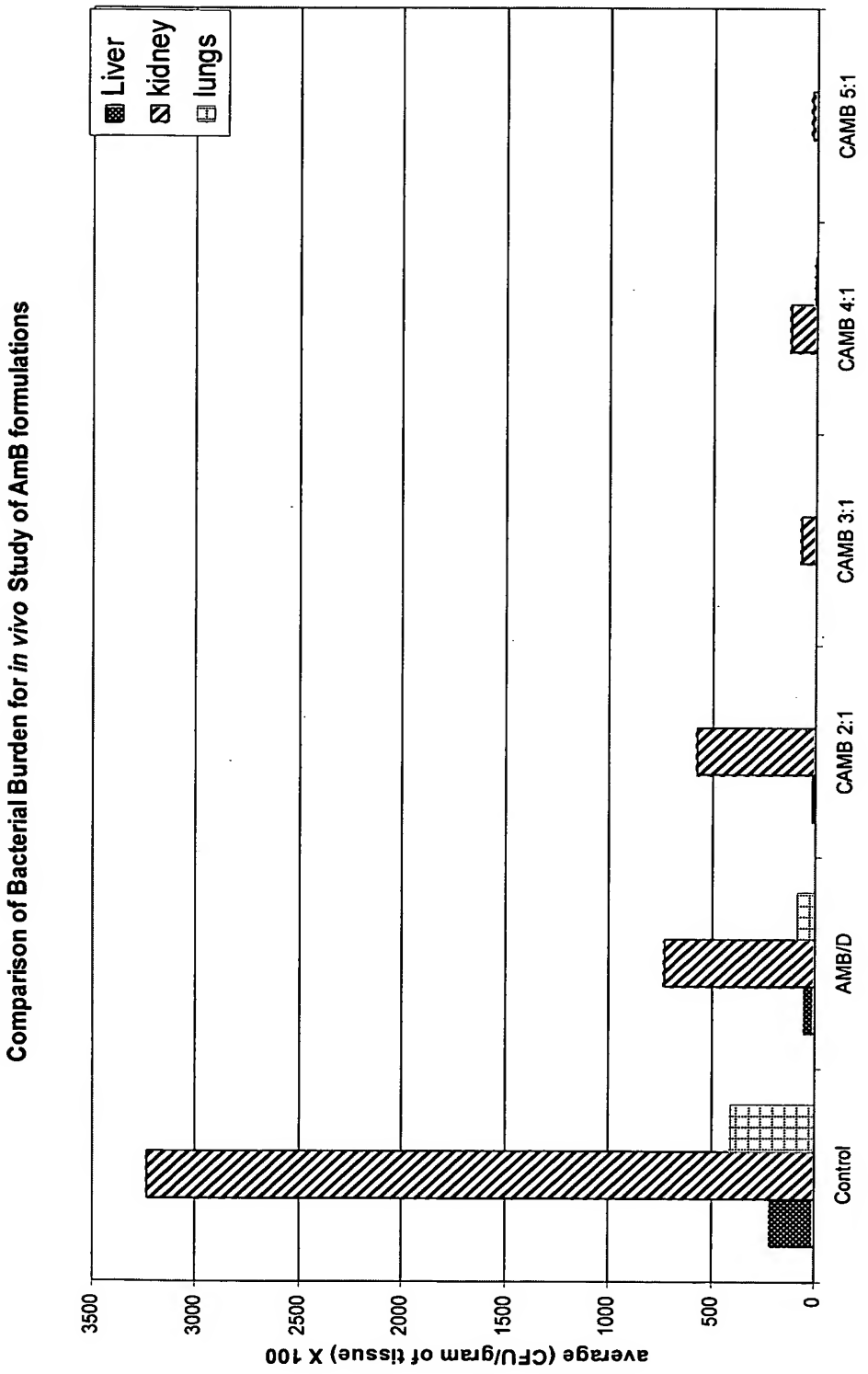

Comparison of Bacterial Burden for *in vivo* Study of AmB formulations
Liver
kidney
lungs
average (CFU/gram of tissue) X 100
3500
3000
2500
2000
1500
1000
500
0
Control
AMB/D
CAMB 2:1
CAMB 3:1
CAMB 4:1
CAMB 5:1

Figure 12

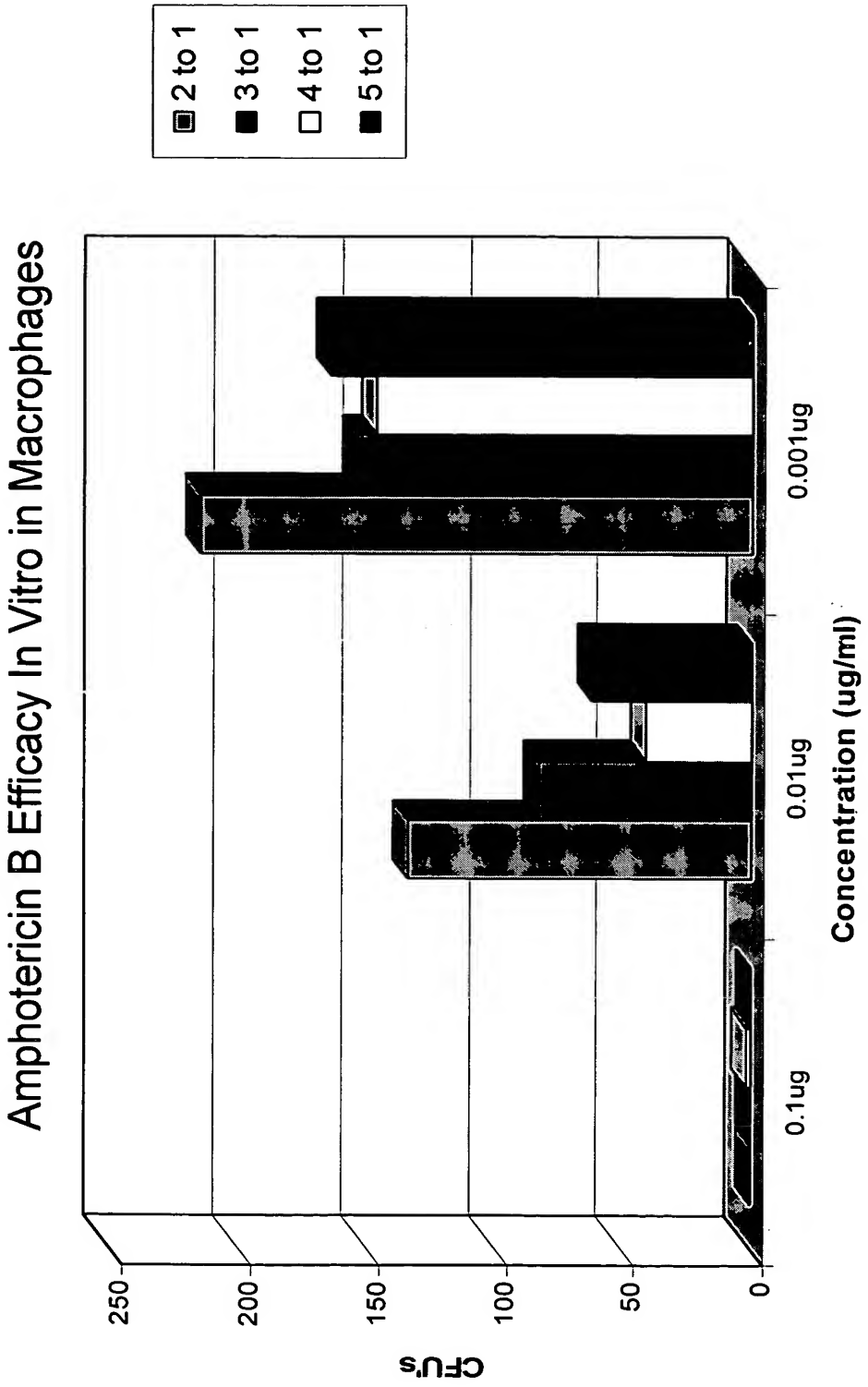
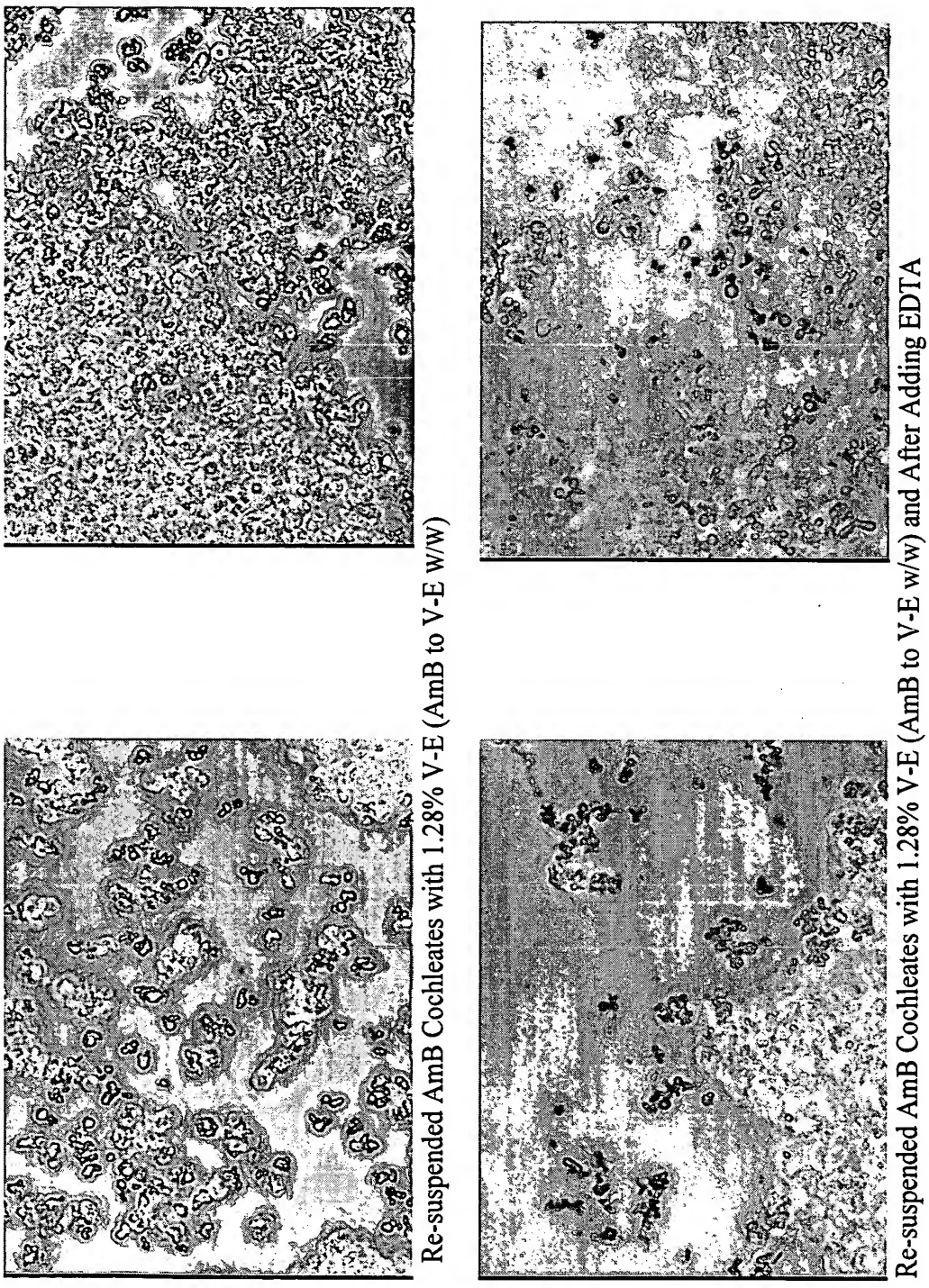

Amphotericin B Efficacy In Vitro in Macrophages
2 to 1
3 to 1
4 to 1
5 to 1
CFU's
250
200
150
100
50
0
0.1ug
0.01ug
0.001ug
Concentration (ug/ml)

Figure 13



Re-suspended AmB Cochleates with 1.28% V-E (AmB to V-E w/w)

Re-suspended AmB Cochleates with 1.28% V-E (AmB to V-E w/w) and After Adding EDTA

Figure 14

SURVIVAL DATA

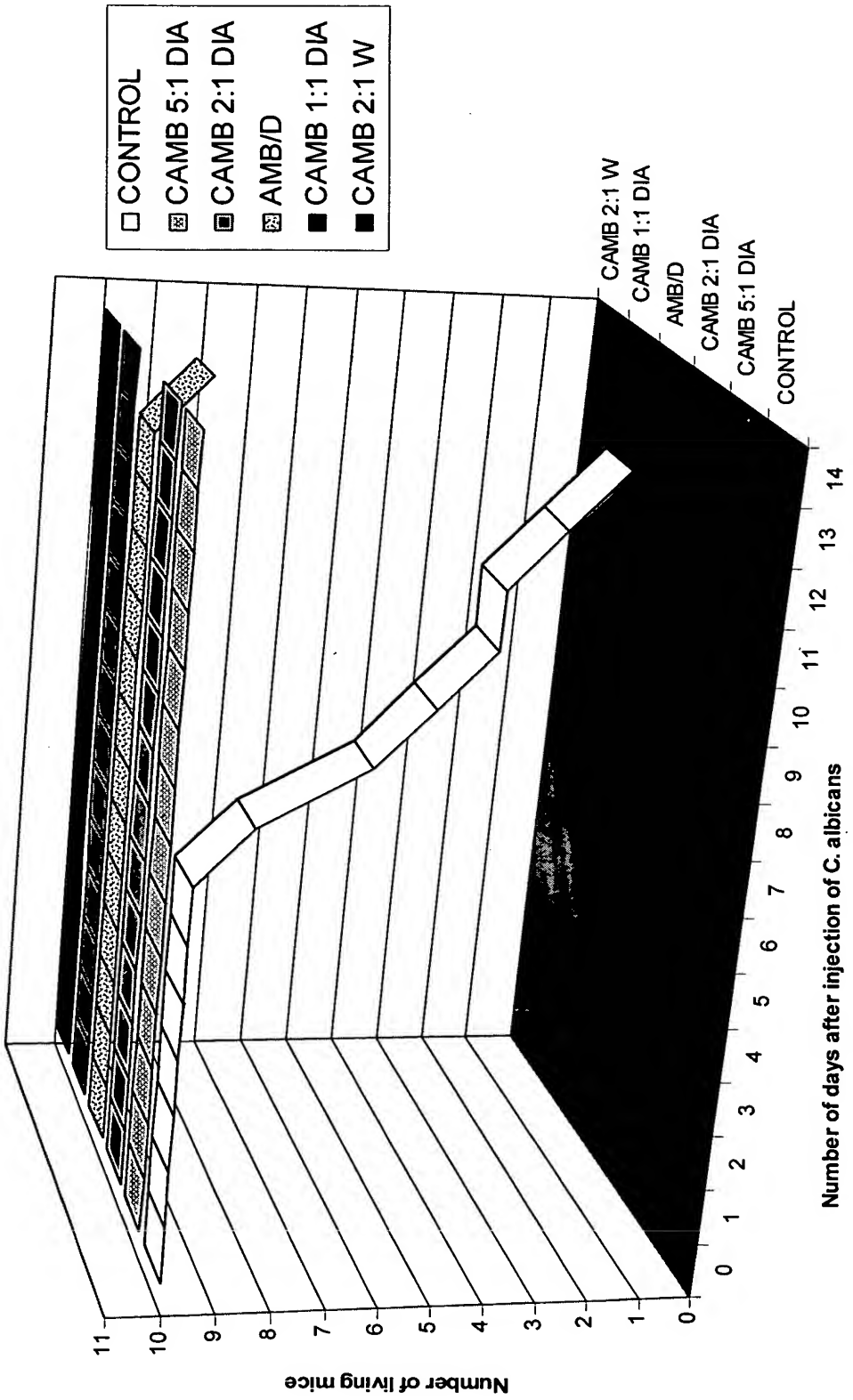


Figure 15

Comparison of Bacterial Burden for in vivo Study of AmB formulations

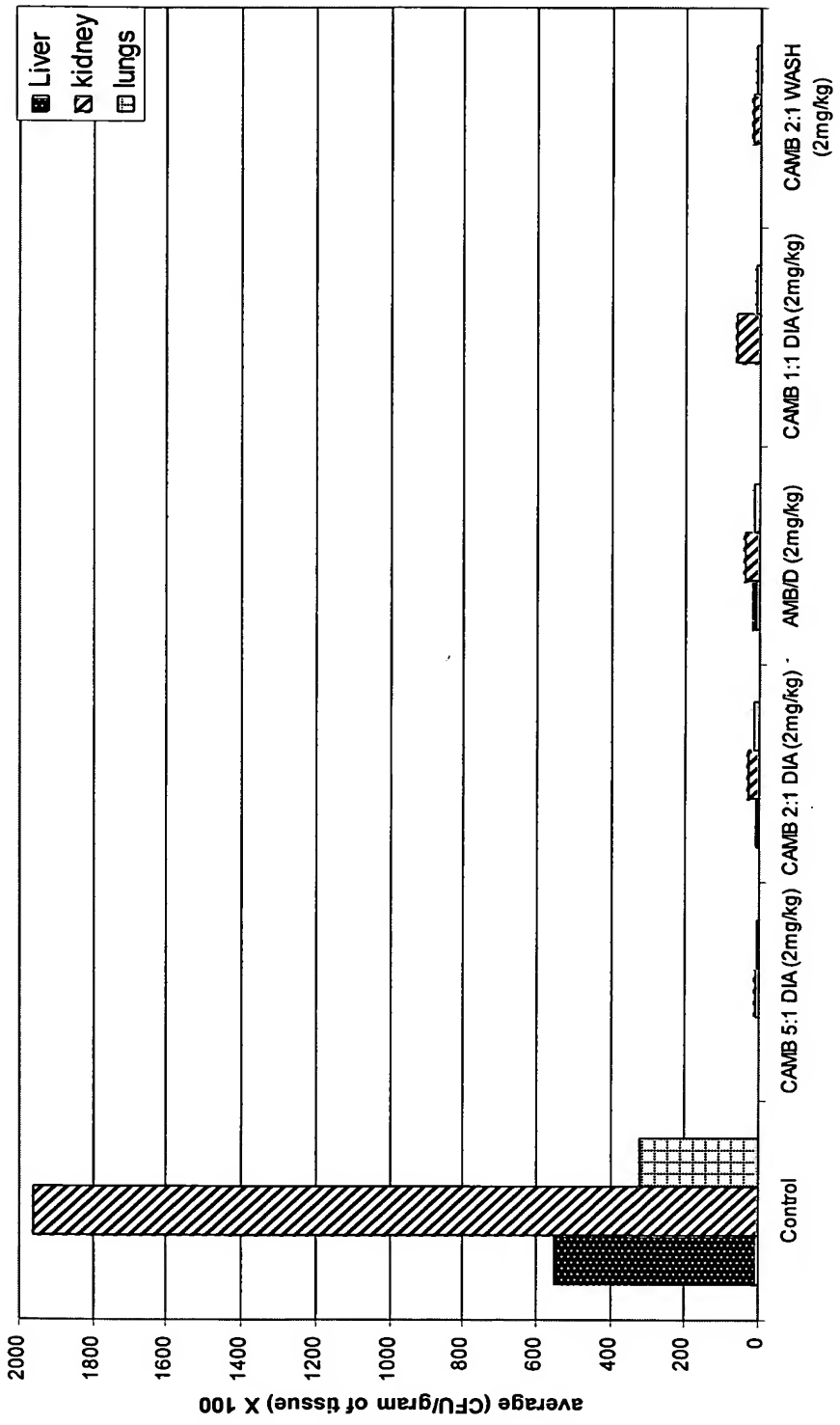


Figure 16

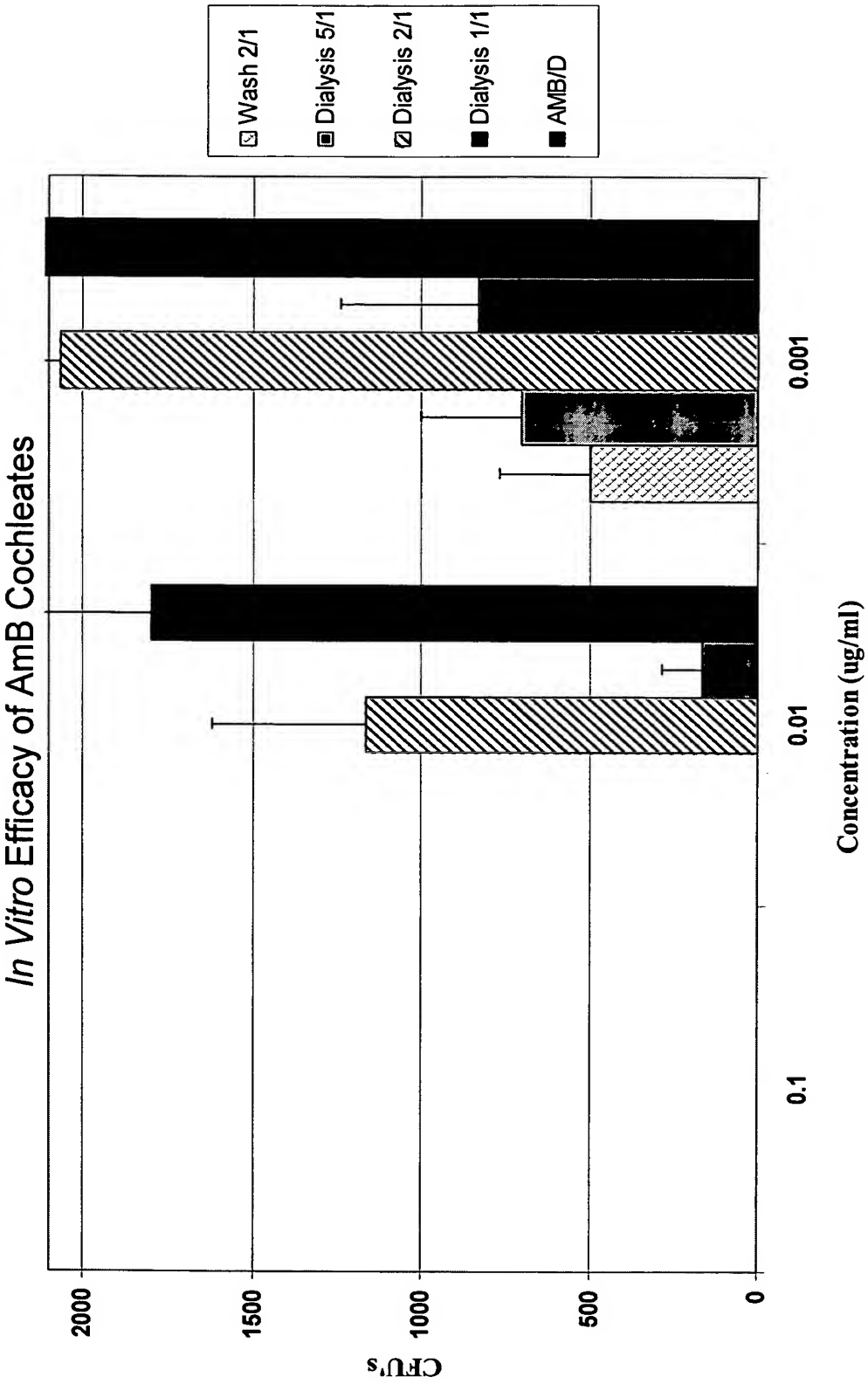

In Vitro Efficacy of AmB Cochleates
Wash 2/1
Dialysis 5/1
Dialysis 2/1
Dialysis 1/1
AMB/D
CFU's
2000
1500
1000
500
0
0.1
0.01
0.001
Concentration (ug/ml)

Figure 17

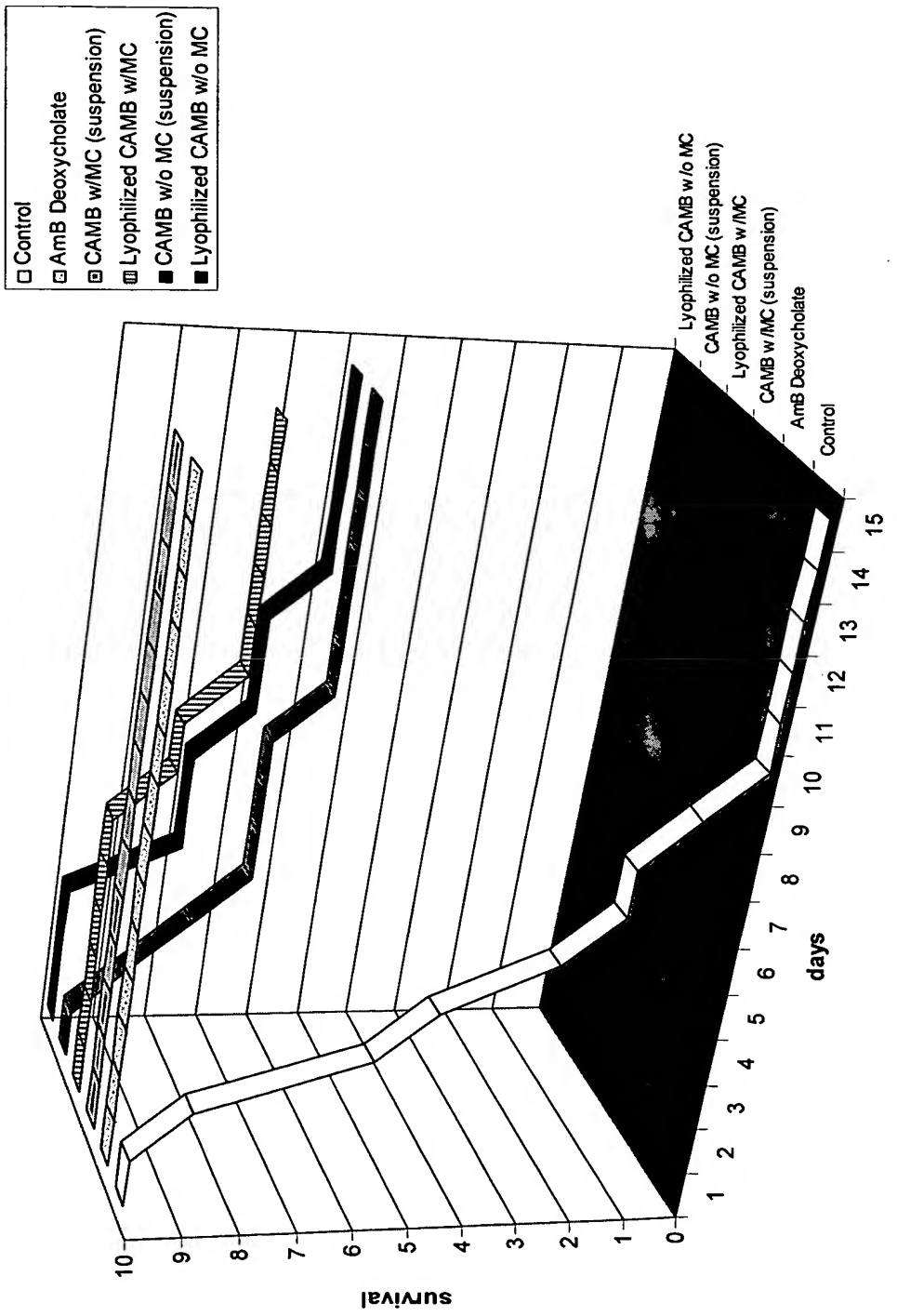

Survival Data
Control
AmB Deoxycholate
CAMB w/MC (suspension)
Lyophilized CAMB w/MC
CAMB w/o MC (suspension)
Lyophilized CAMB w/o MC
survival
0
1
2
3
4
5
6
7
8
9
10
days
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Lyophilized CAMB w/o MC
CAMB w/o MC (suspension)
Lyophilized CAMB w/MC
CAMB w/MC (suspension)
AmB Deoxycholate
Control

Figure 18

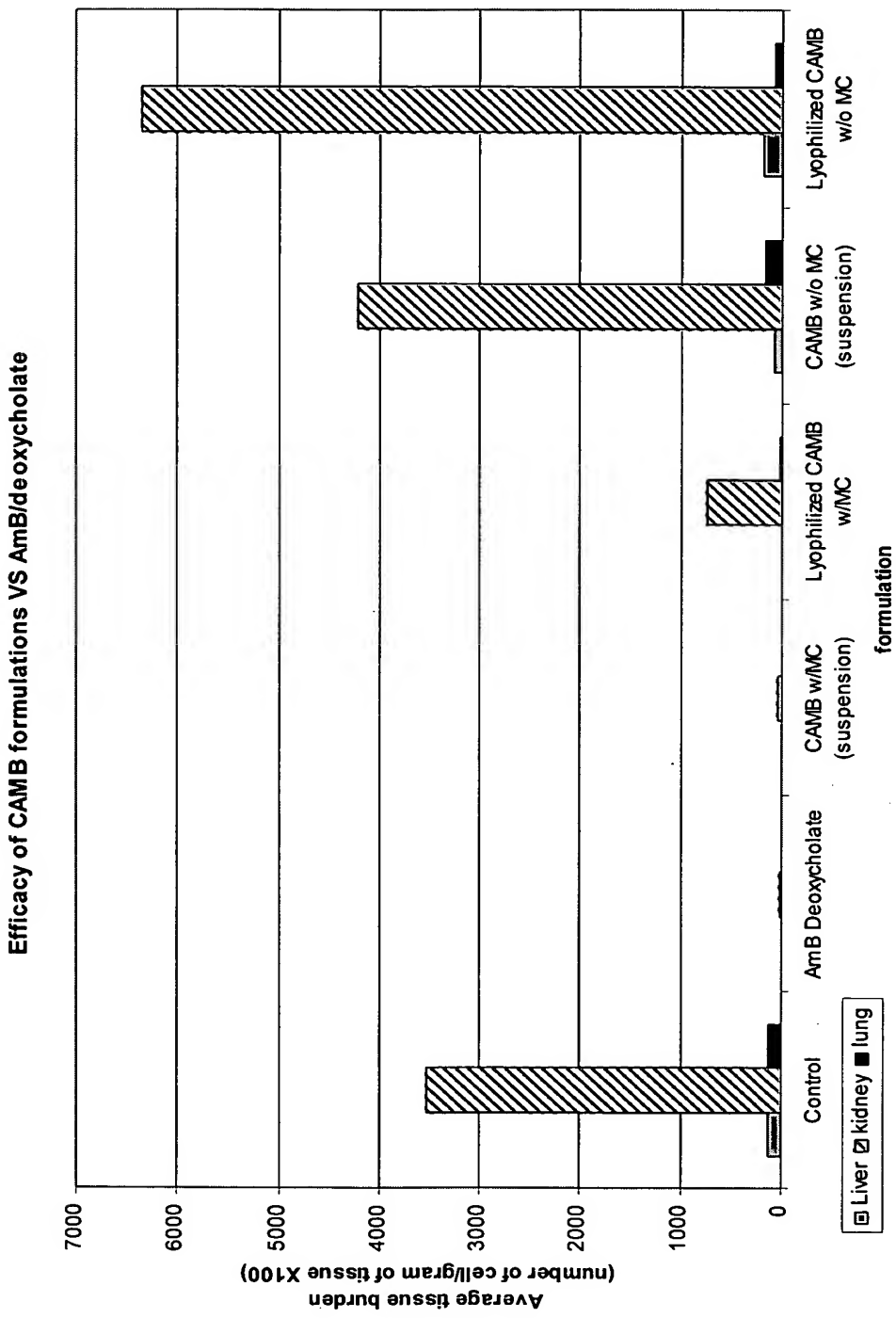

Efficacy of CAMB formulations VS AmB/deoxycholate
Average tissue burden
(number of cell/gram of tissue X100)
7000
6000
5000
4000
3000
2000
1000
0
Control
AmB Deoxycholate
CAMB w/MC (suspension)
Lyophilized CAMB w/MC
CAMB w/o MC (suspension)
Lyophilized CAMB w/o MC
formulation
Liver
kidney
lung

Figure 19

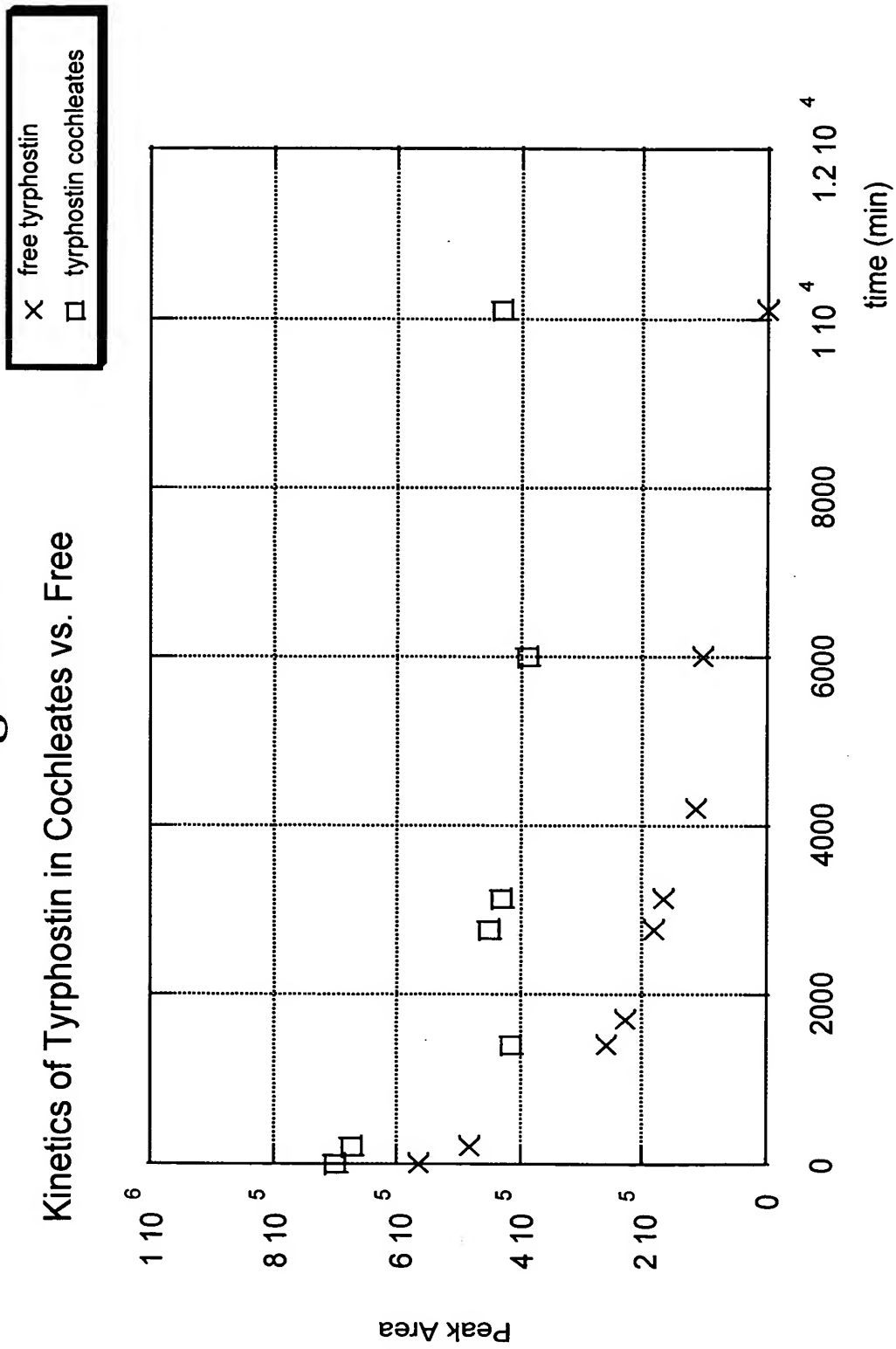

Kinetics of Tyrphostin in Cochleates vs. Free
free tyrphostin
tyrphostin cochleates
Peak Area
1 10^6
8 10^5
6 10^5
4 10^5
2 10^5
0
0
2000
4000
6000
8000
1 10^4
1.2 10^4
time (min)

Figure 20

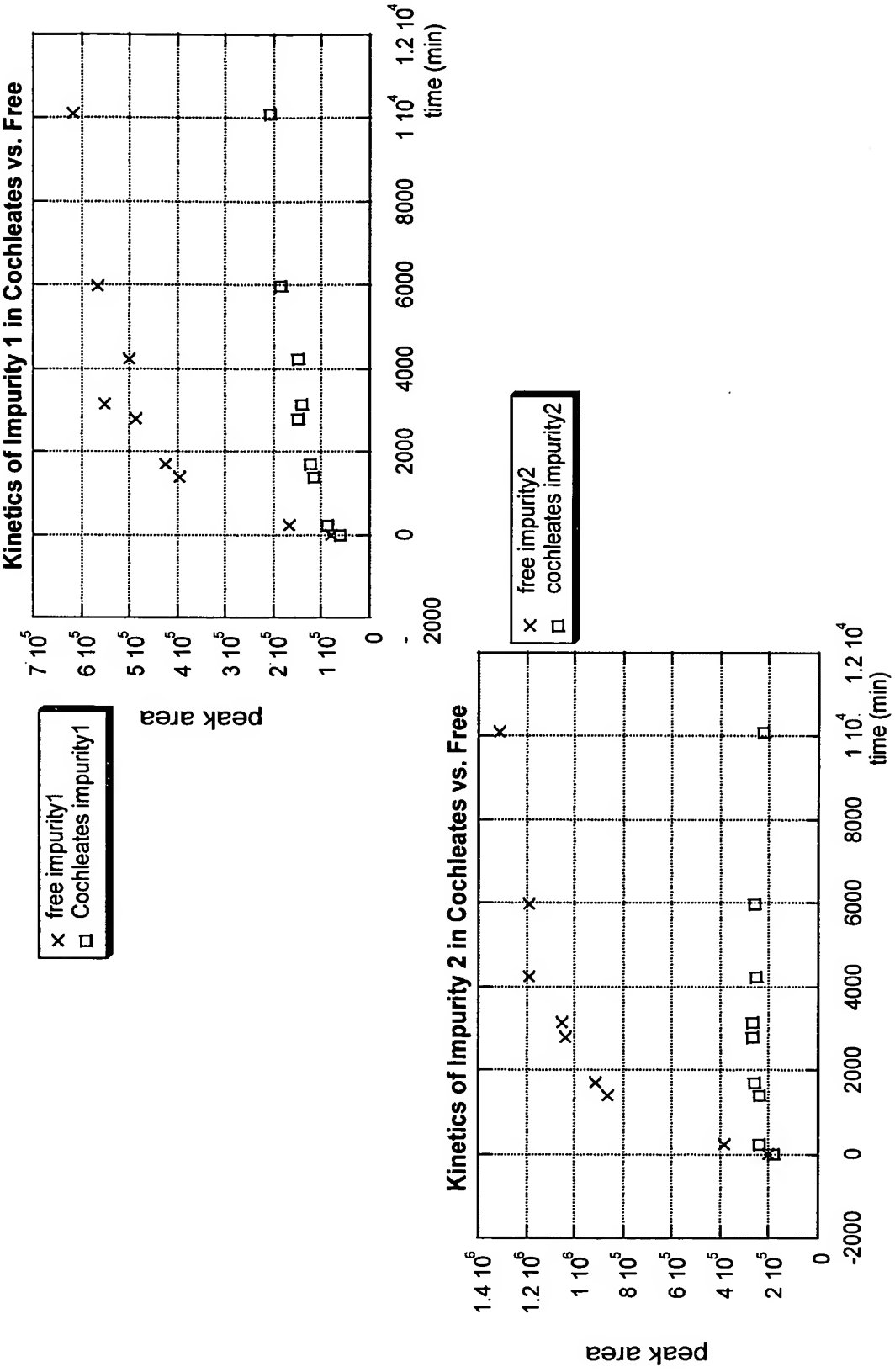

Kinetics of Impurity 1 in Cochleates vs. Free
peak area
time (min)
free impurity1
Cochleates impurity1
Kinetics of Impurity 2 in Cochleates vs. Free
peak area
time (min)
free impurity2
cochleates impurity2

Figure 21

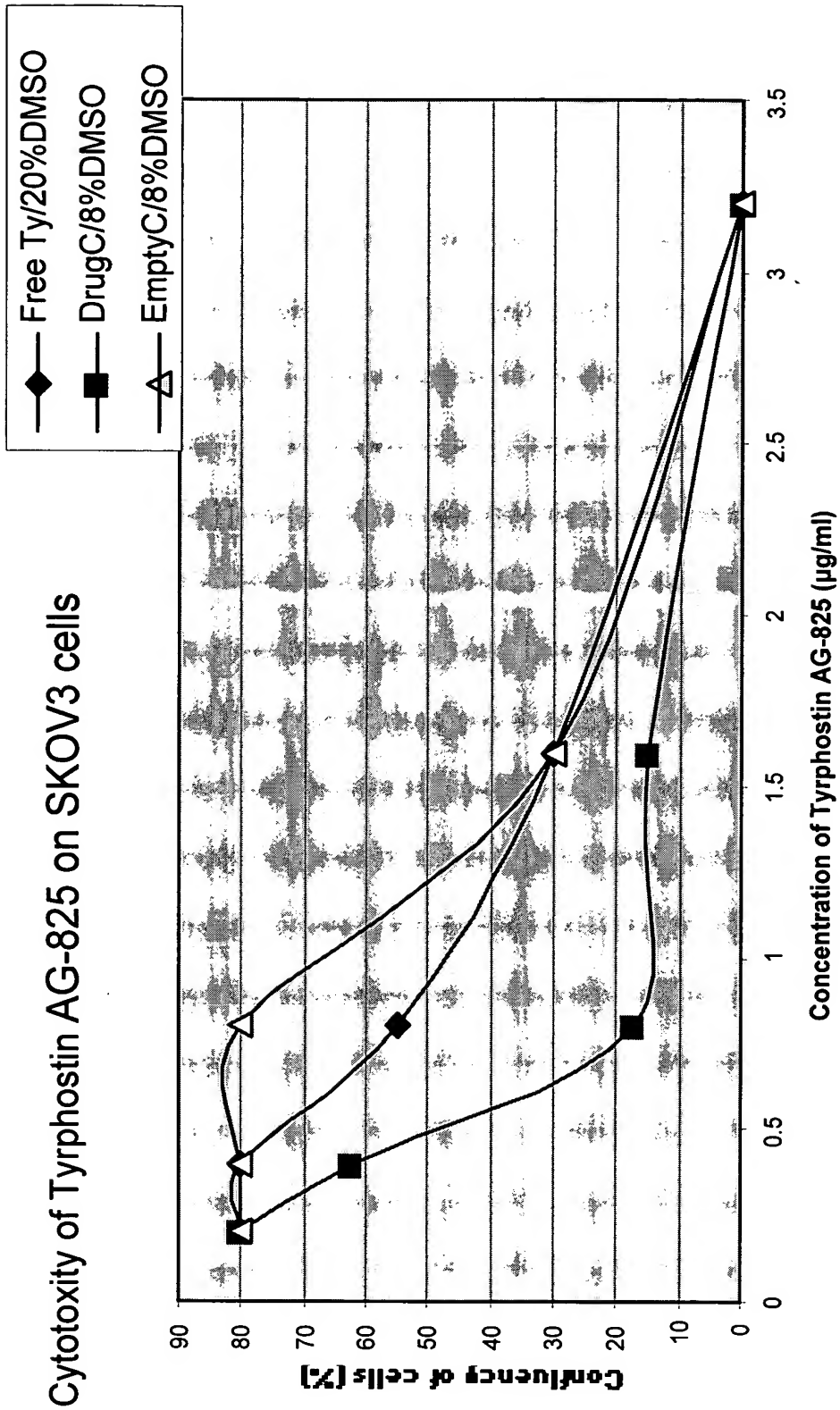

Cytotoxity of Tyrphostin AG-825 on SKOV3 cells
Free Ty/20%DMSO
DrugC/8%DMSO
EmptyC/8%DMSO
Confluency of cells (%)
90
80
70
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
3.5
Concentration of Tyrphostin AG-825 (µg/ml)

Figure 22

ZnTPP In solution in 100% DMSO and in Cochleates

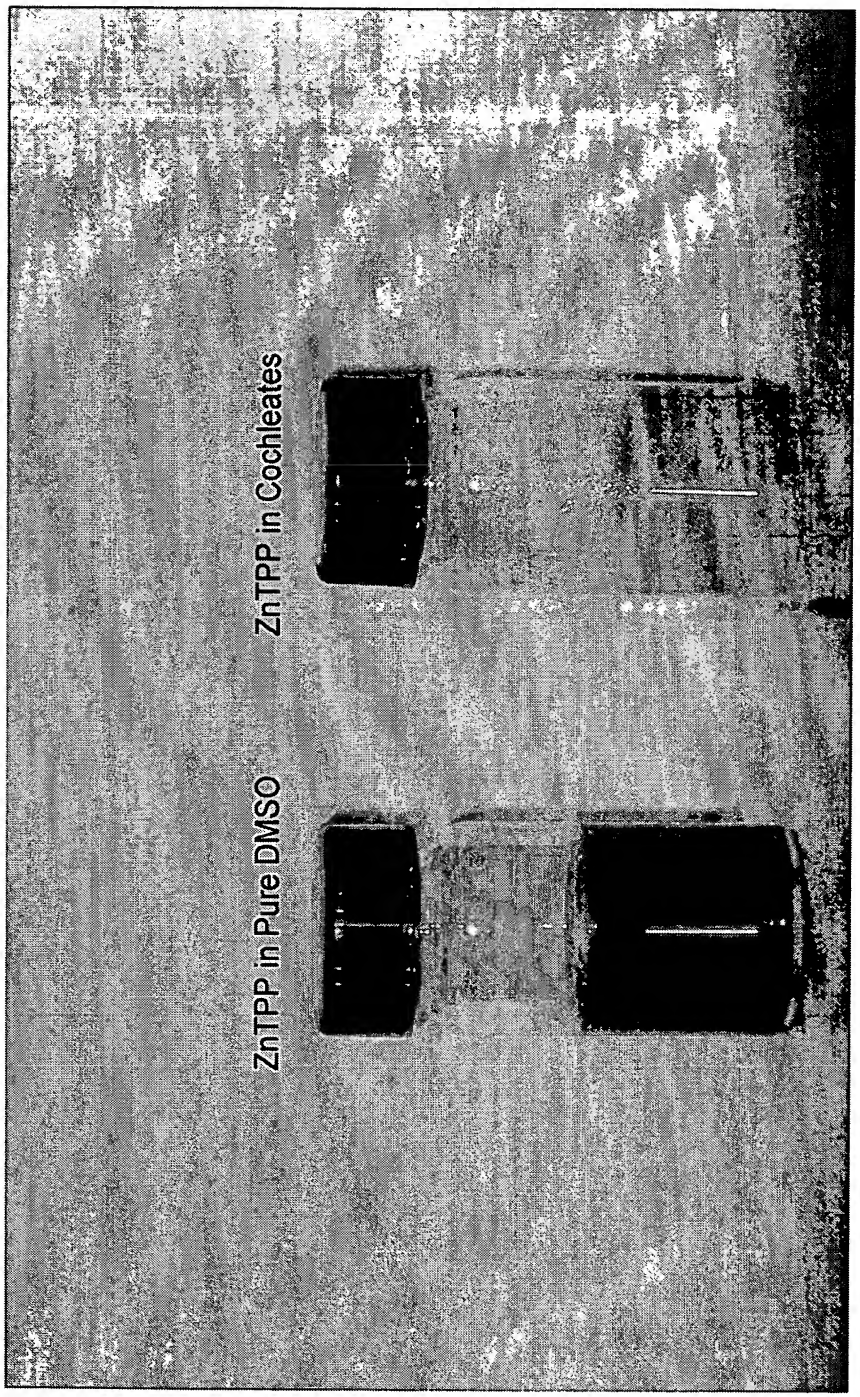


Figure 23

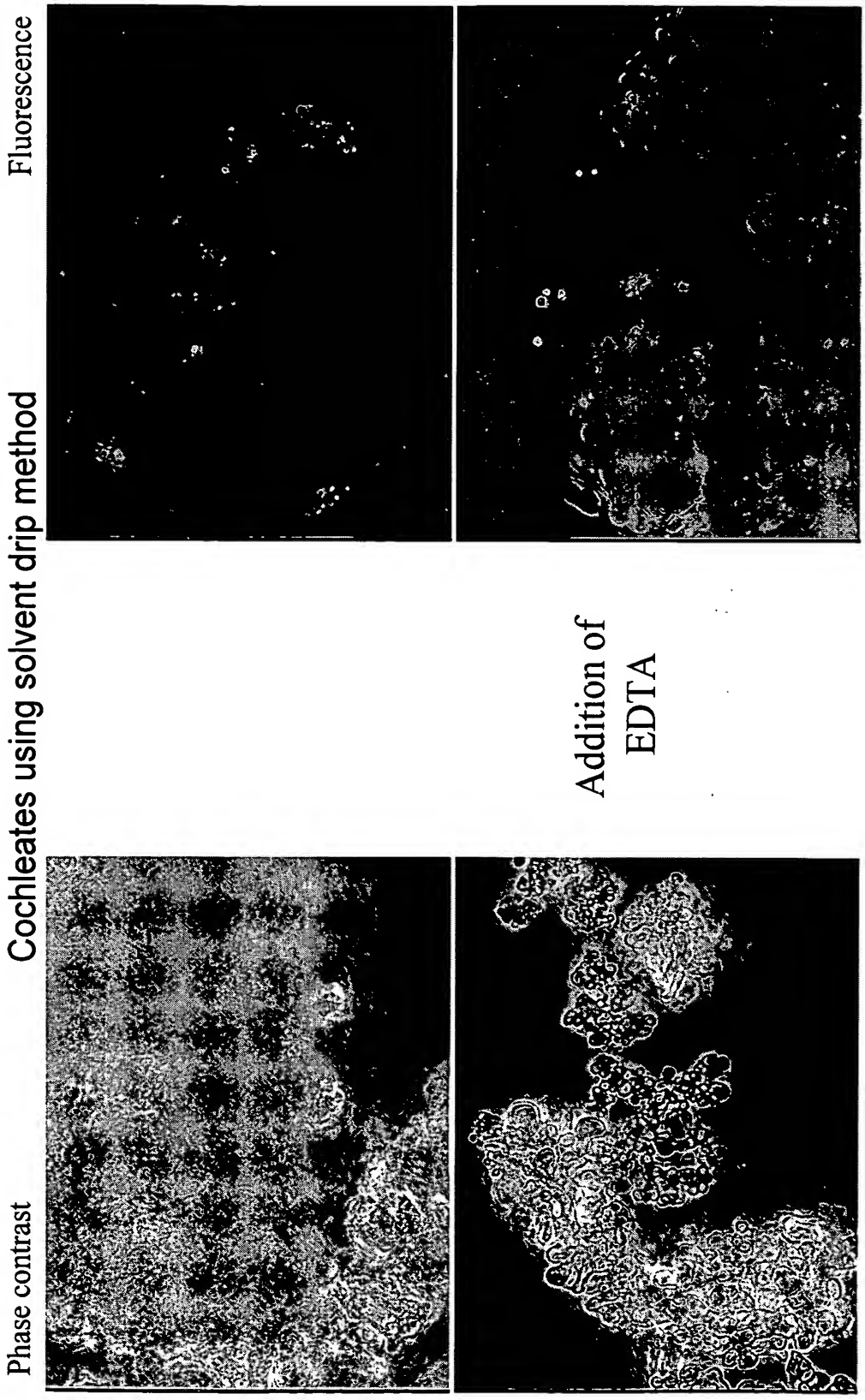

Cochleates using solvent drip method
Fluorescence
Phase contrast
Addition of EDTA

Figure 24

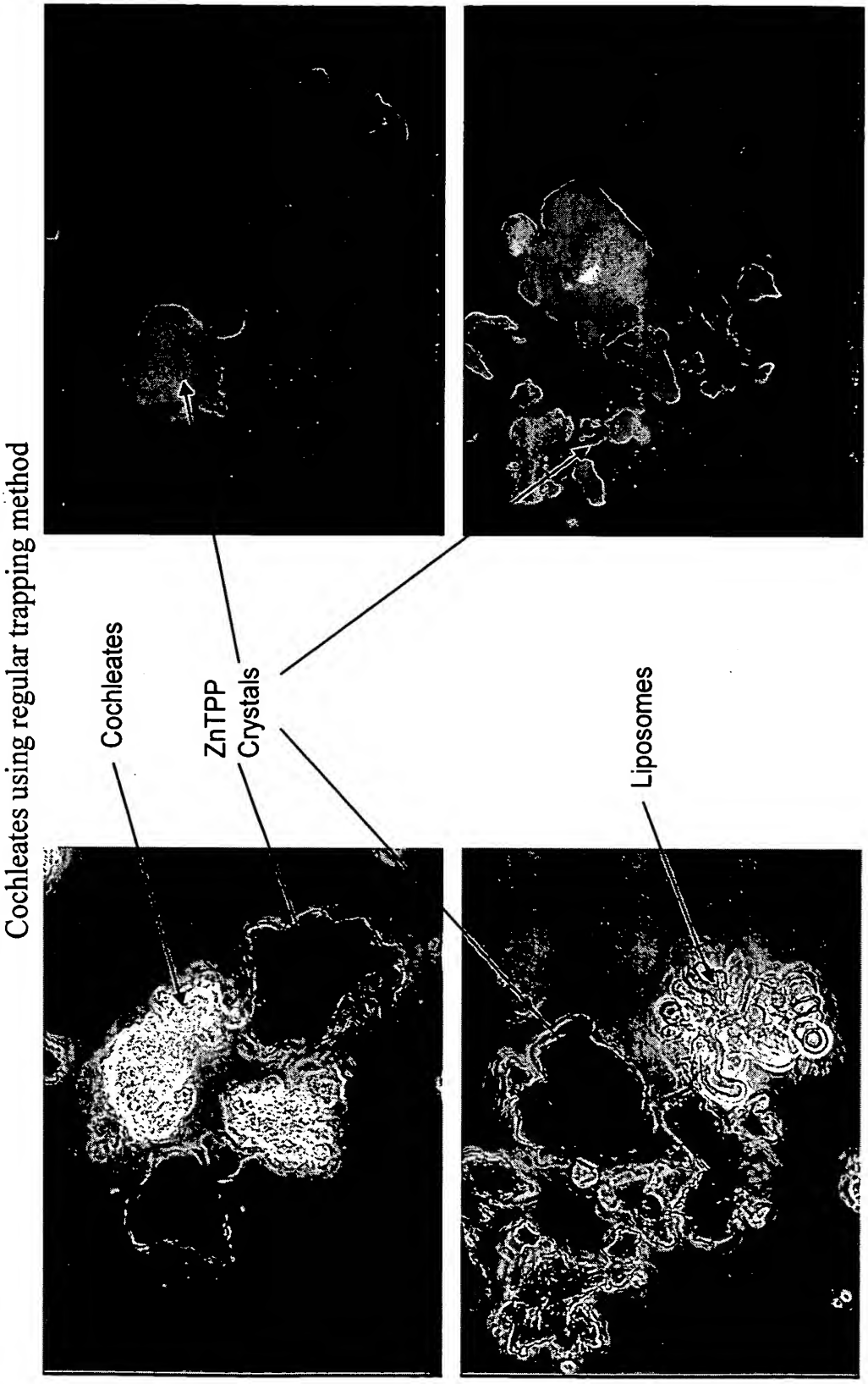

Cochleates using regular trapping method
Cochleates
ZnTPP Crystals
Liposomes

Figure 25

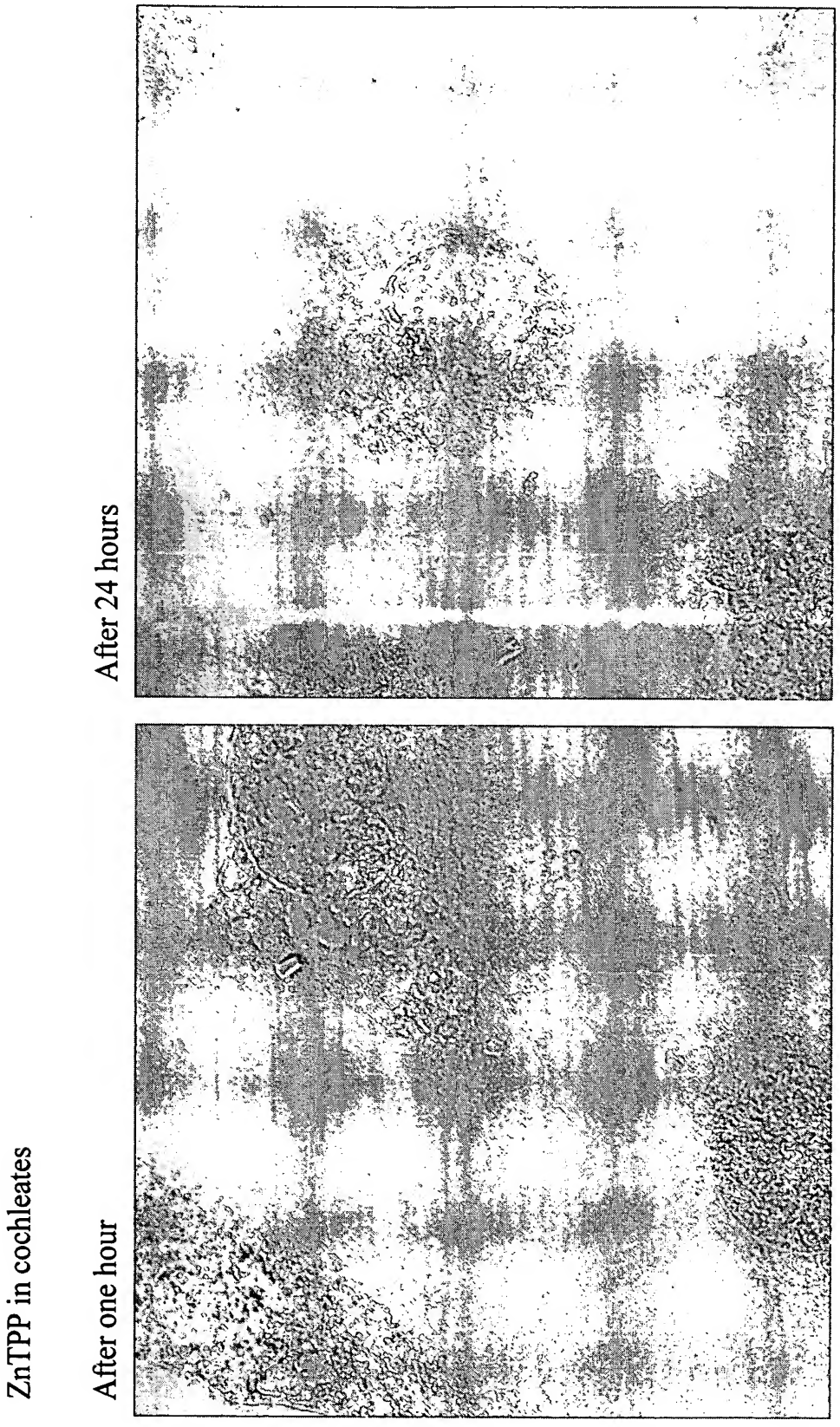


Figure 26

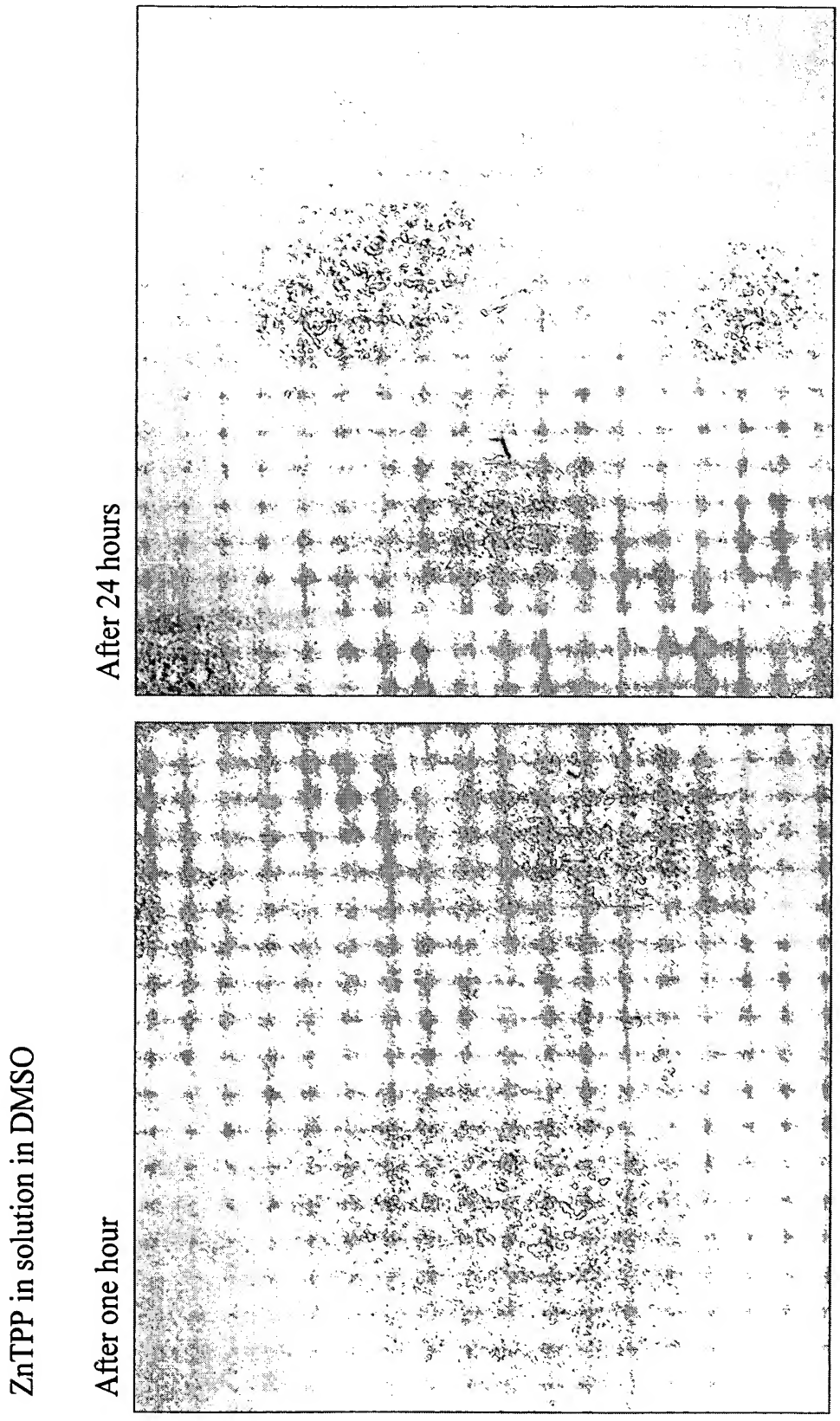


Figure 27

Cochleates containing Pyrene DOPE

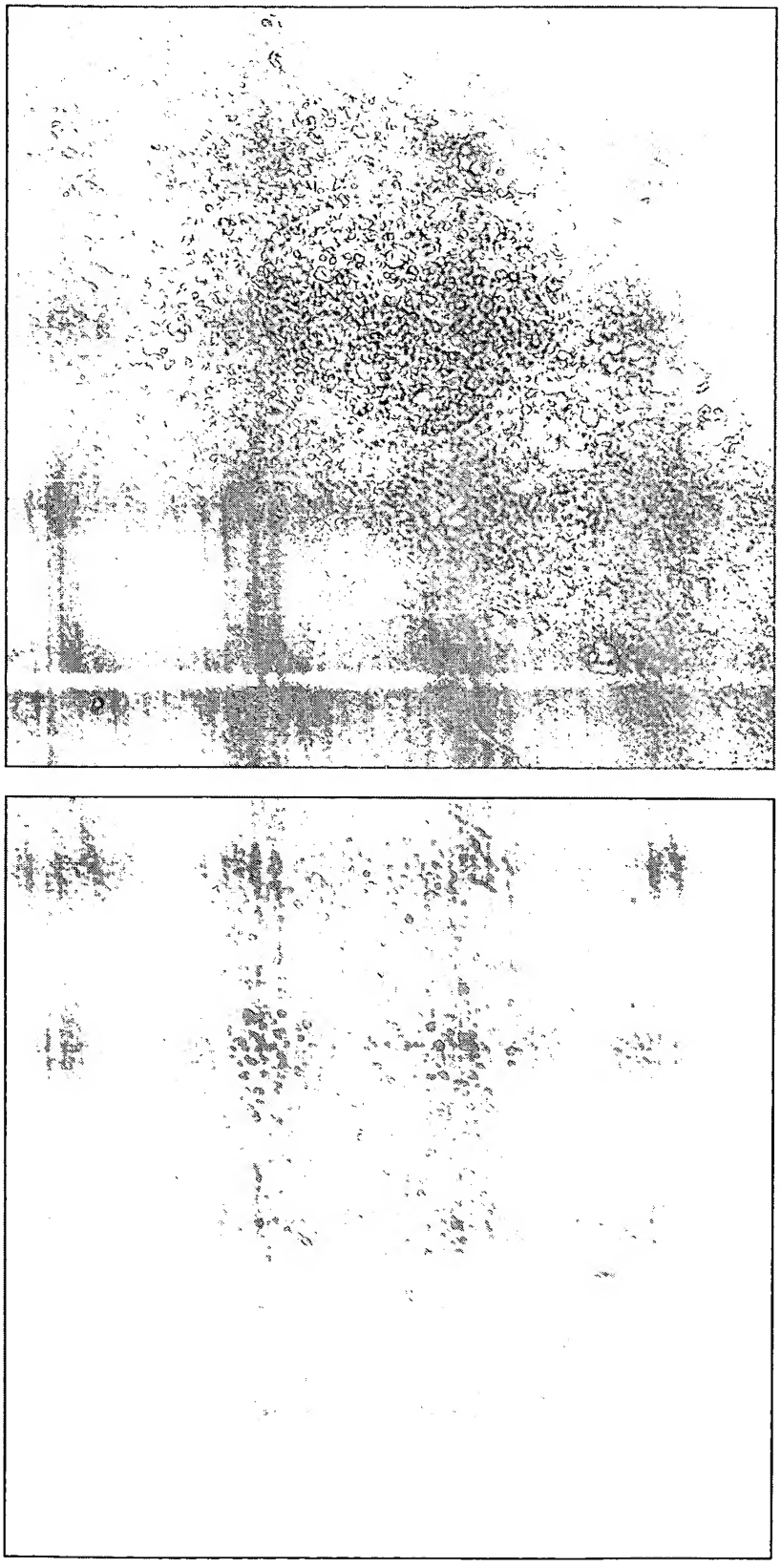


Figure 28

Cochleates containing Pyrene DOPE and ZnTPP

After 24 hours

After 1 hour

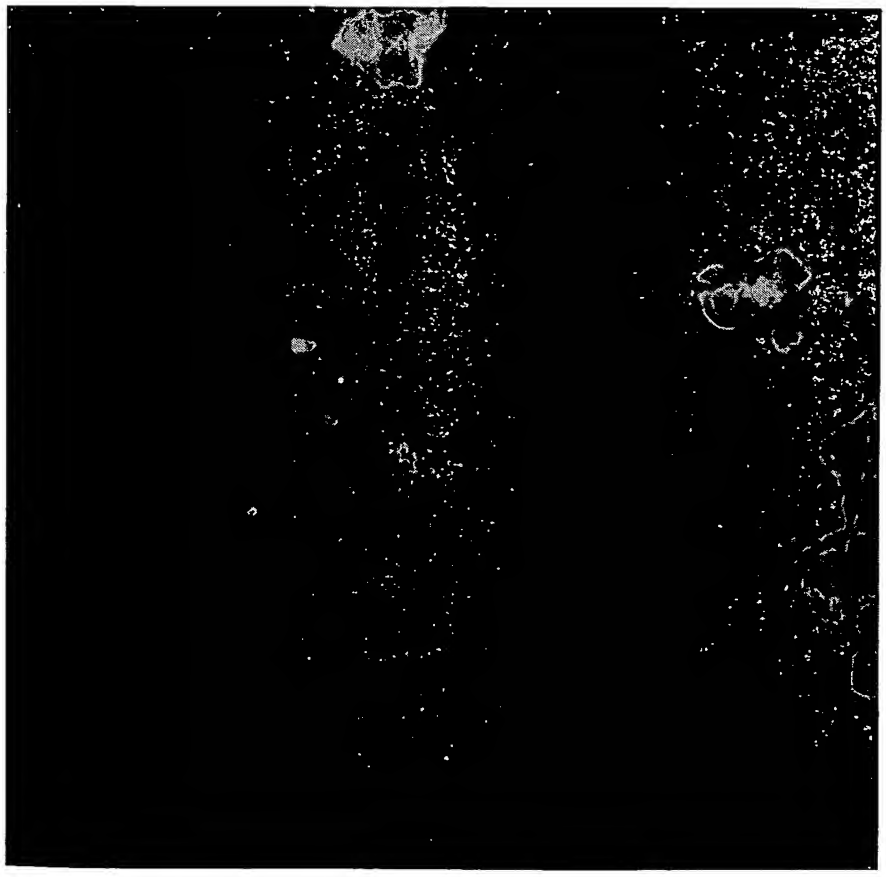
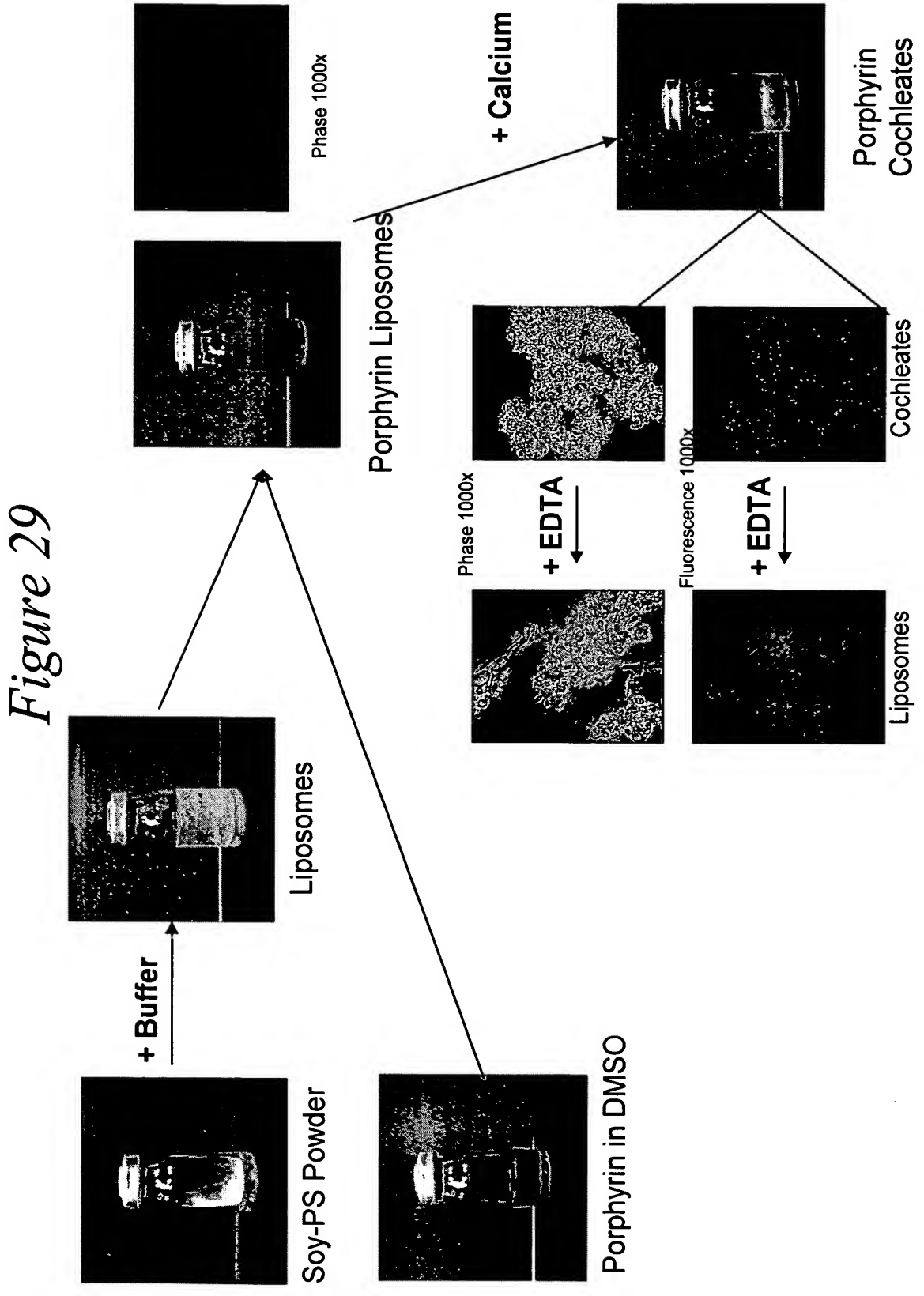
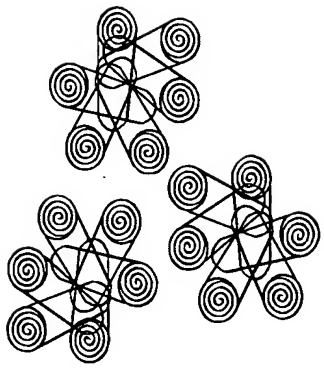


Figure 29


Phase 1000x
+ Calcium
Porphyrin Cochleates
Porphyrin Liposomes
Phase 1000x
+ EDTA
Fluorescence 1000x
+ EDTA
Cochleates
Liposomes
+ Buffer
Liposomes
Soy-PS Powder
Porphyrin in DMSO



Aqueous Buffer

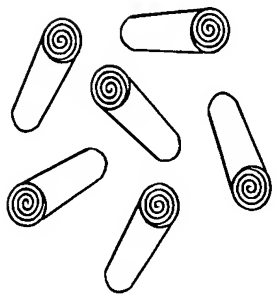
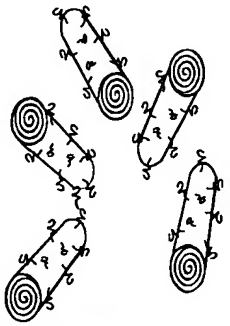


Figure 30



Cation

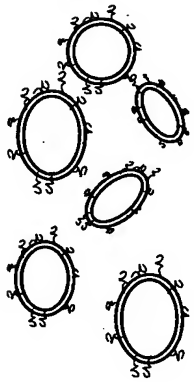
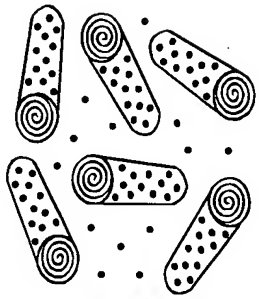


Figure 31



Aggregation Inhibitors

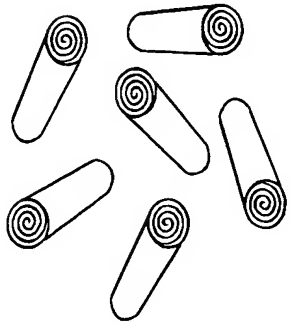


Figure 32

Phase Contrast and Fluorescence

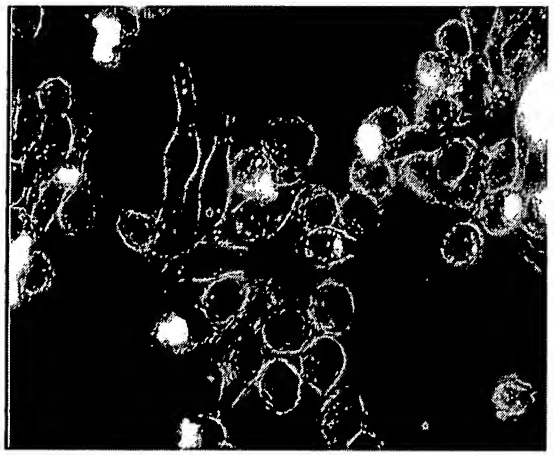


Figure 33A

***In vitro* uptake of Rho-PE-lipid precipitates**

Lipid Precipitates Without Aggregation Inhibitor

Fluorescence

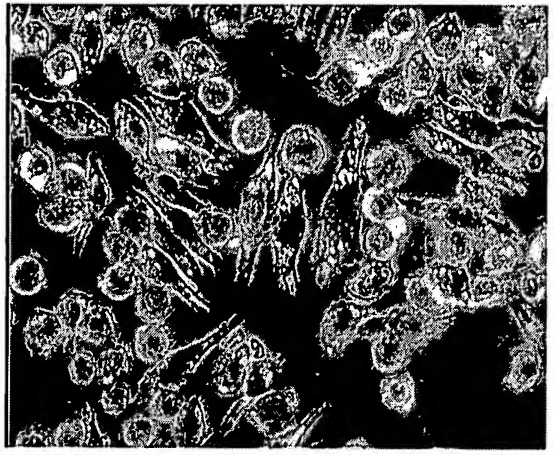


Figure 33B

***In vitro* uptake of Rho-PE-lipid precipitates**

Lipid Precipitates With Aggregation Inhibitor

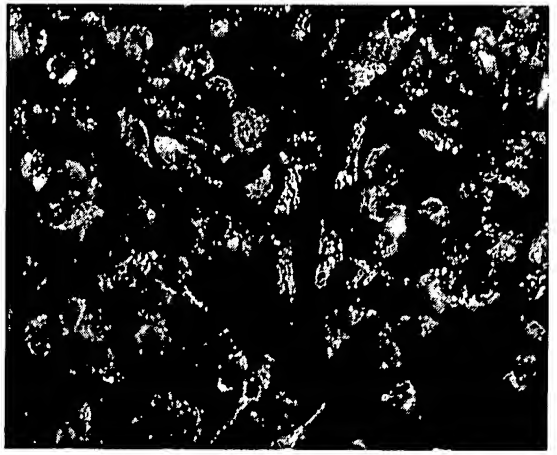


Figure 34B

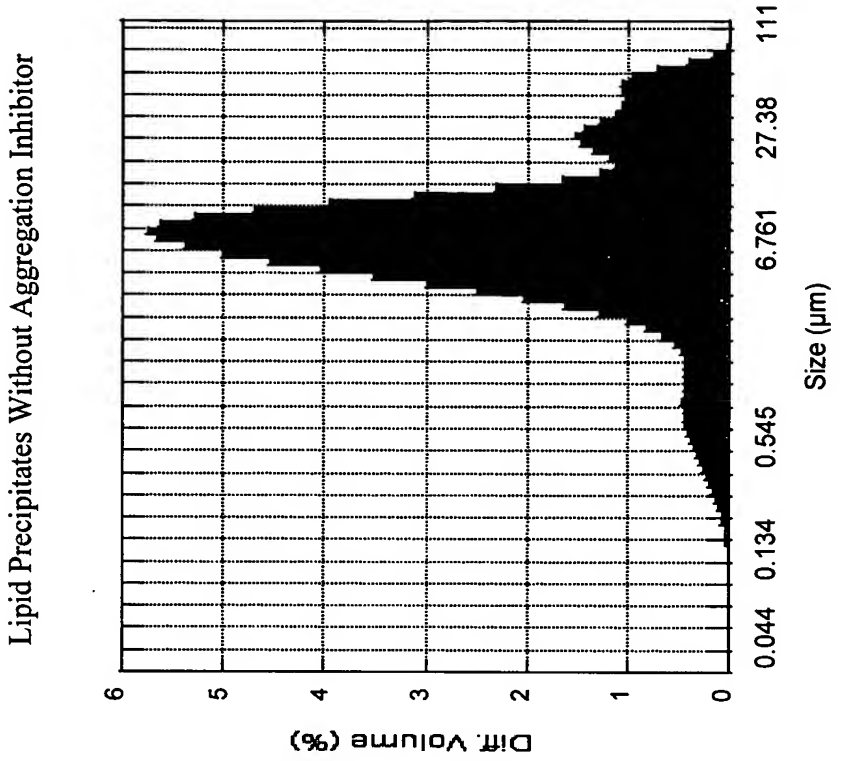


Figure 34A

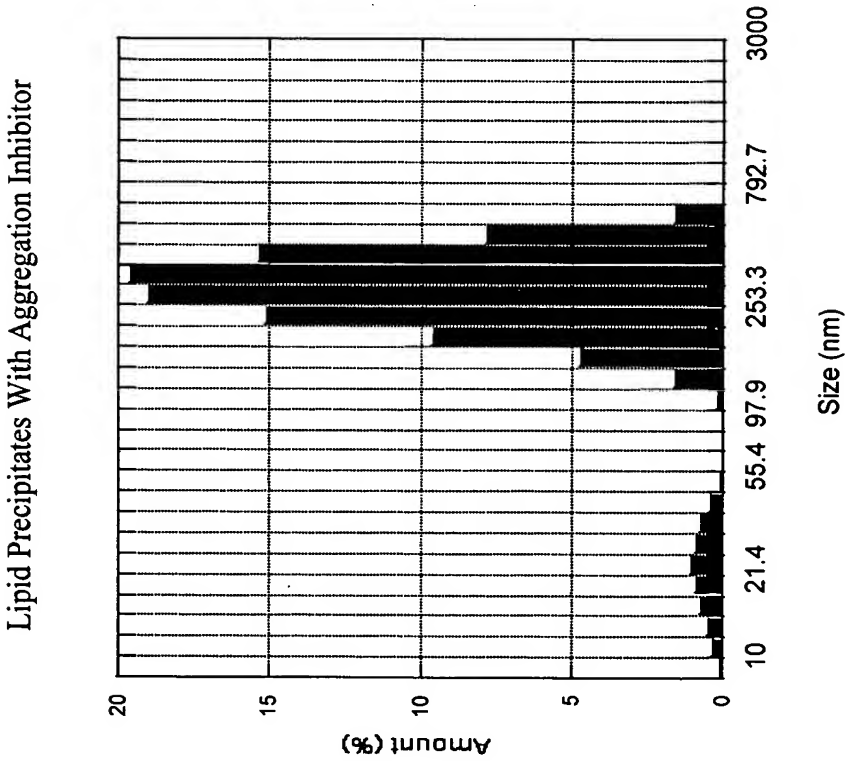


Figure 35

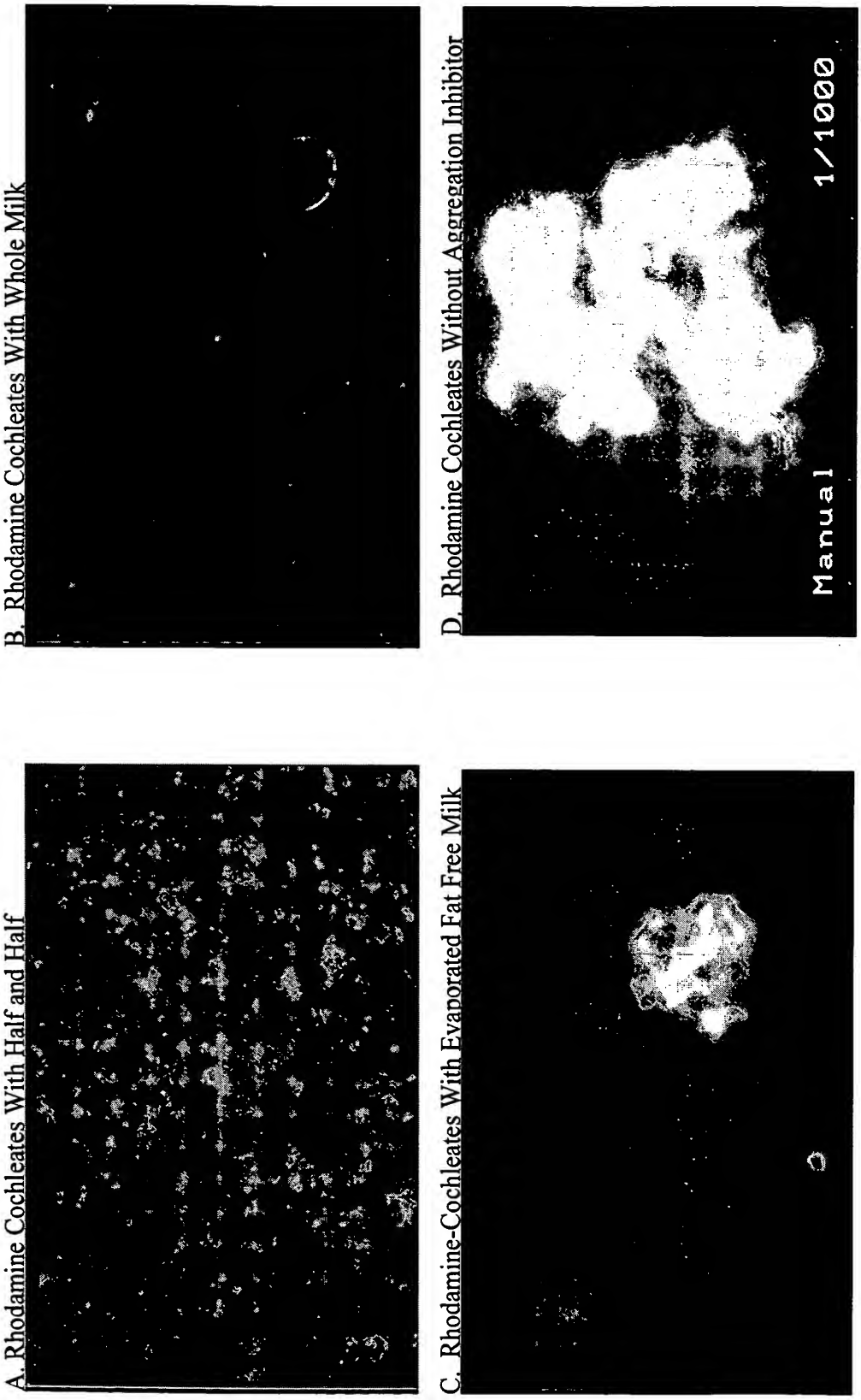

B. Rhodamine Cochleates With Whole Milk
D. Rhodamine Cochleates Without Aggregation Inhibitor
1/1000
Manual
A. Rhodamine Cochleates With Half and Half
C. Rhodamine-Cochleates With Evaporated Fat Free Milk

Figure 36

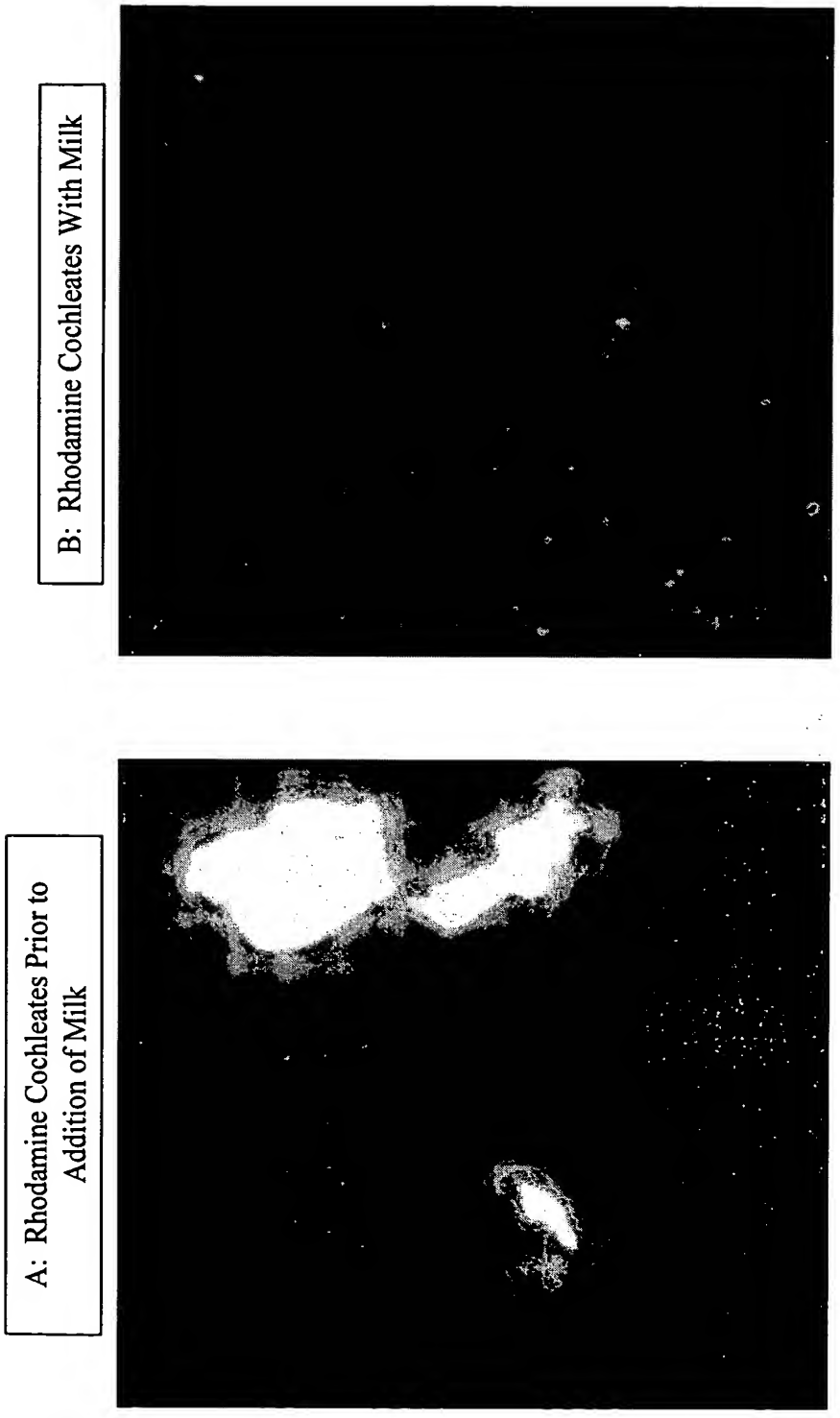
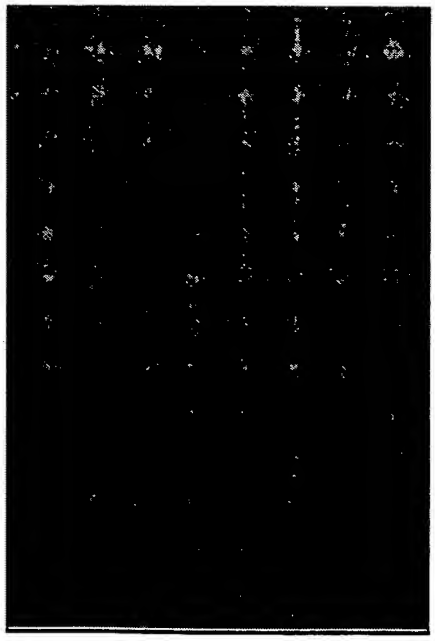

B: Rhodamine Cochleates With Milk
A: Rhodamine Cochleates Prior to Addition of Milk

Figure 37A

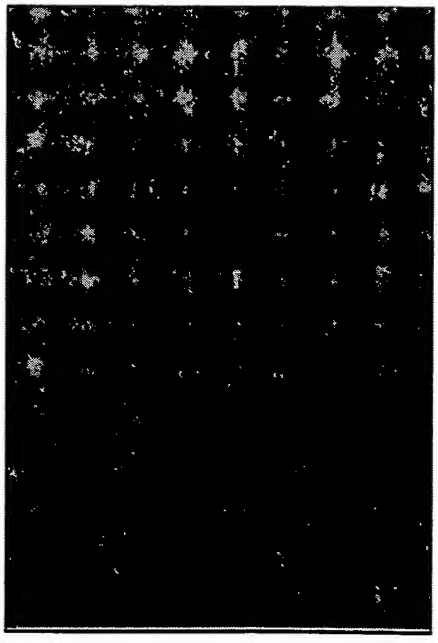
Acetaminophen Lipid Precipitates Without Casein



Acetaminophen Lipid Precipitates With Casein

Figure 37B

Aspirin Lipid Precipitates Without Casein



Aspirin Lipid Precipitates With Casein

Figure 38

Comparison of *In Vivo* Efficacy of Aspirin Formulations in Mice (Right Hind Paw)

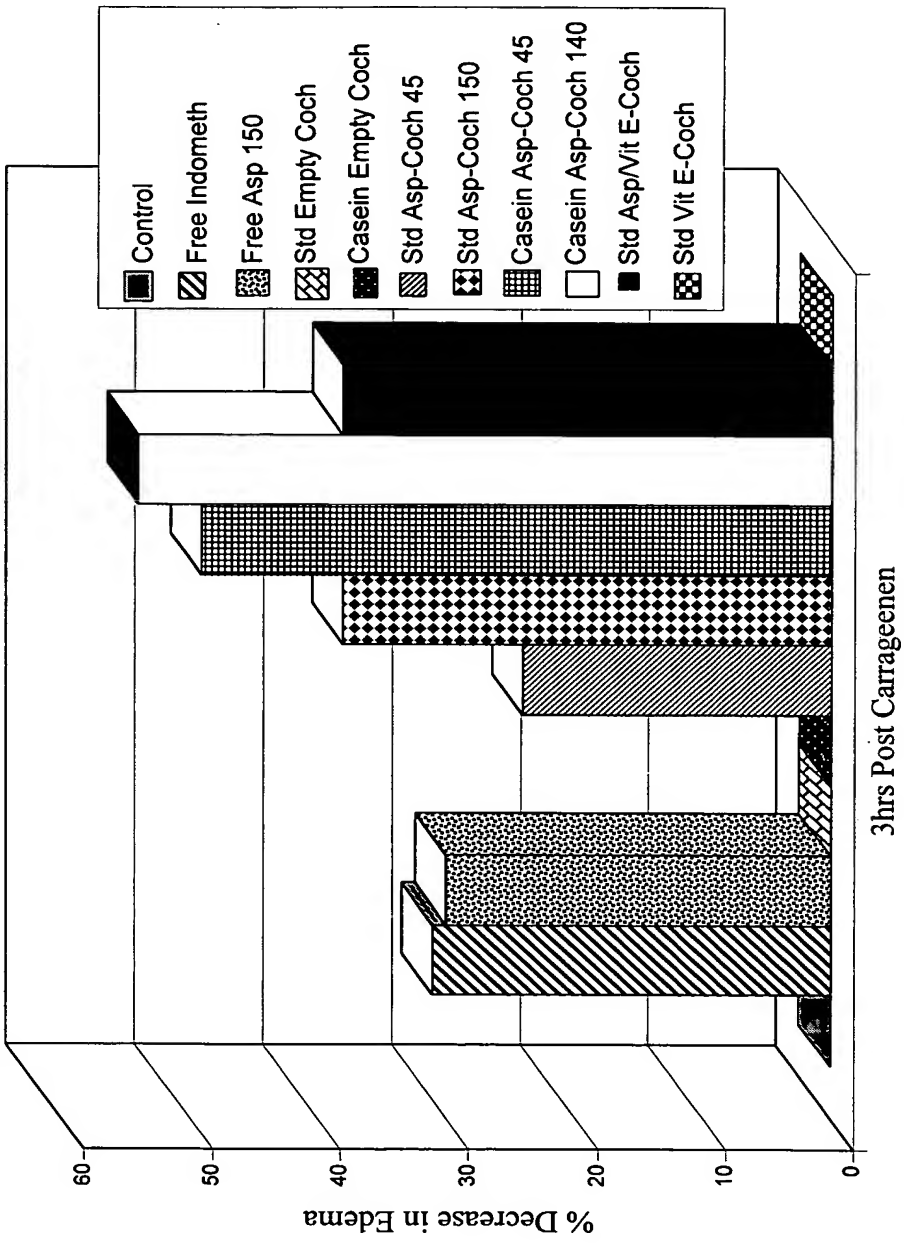


Figure 39

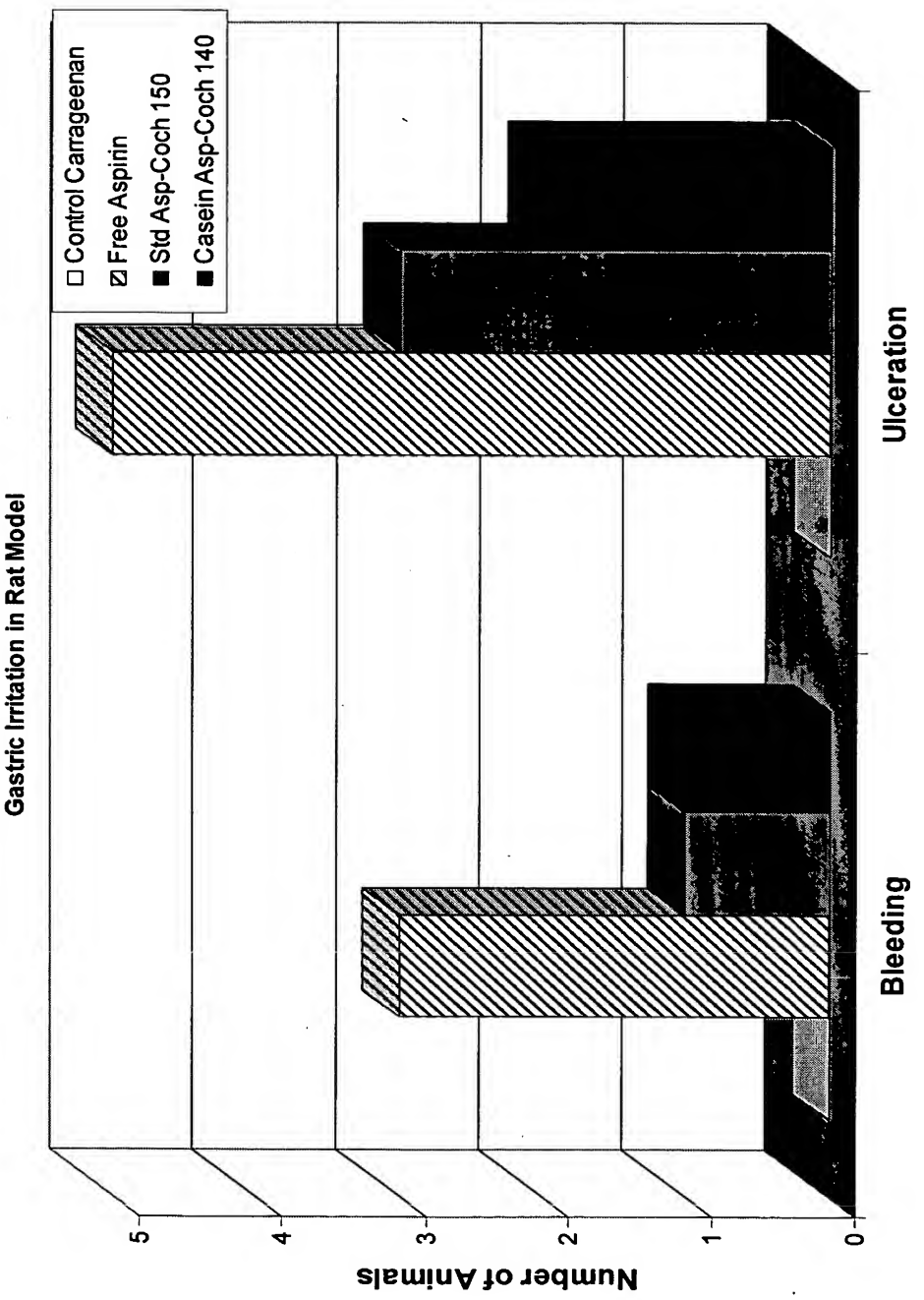

Gastric Irritation in Rat Model
Control Carrageenan
Free Aspirin
Std Asp-Coch 150
Casein Asp-Coch 140
Number of Animals
0
1
2
3
4
5
Bleeding
Ulceration

Figure 40

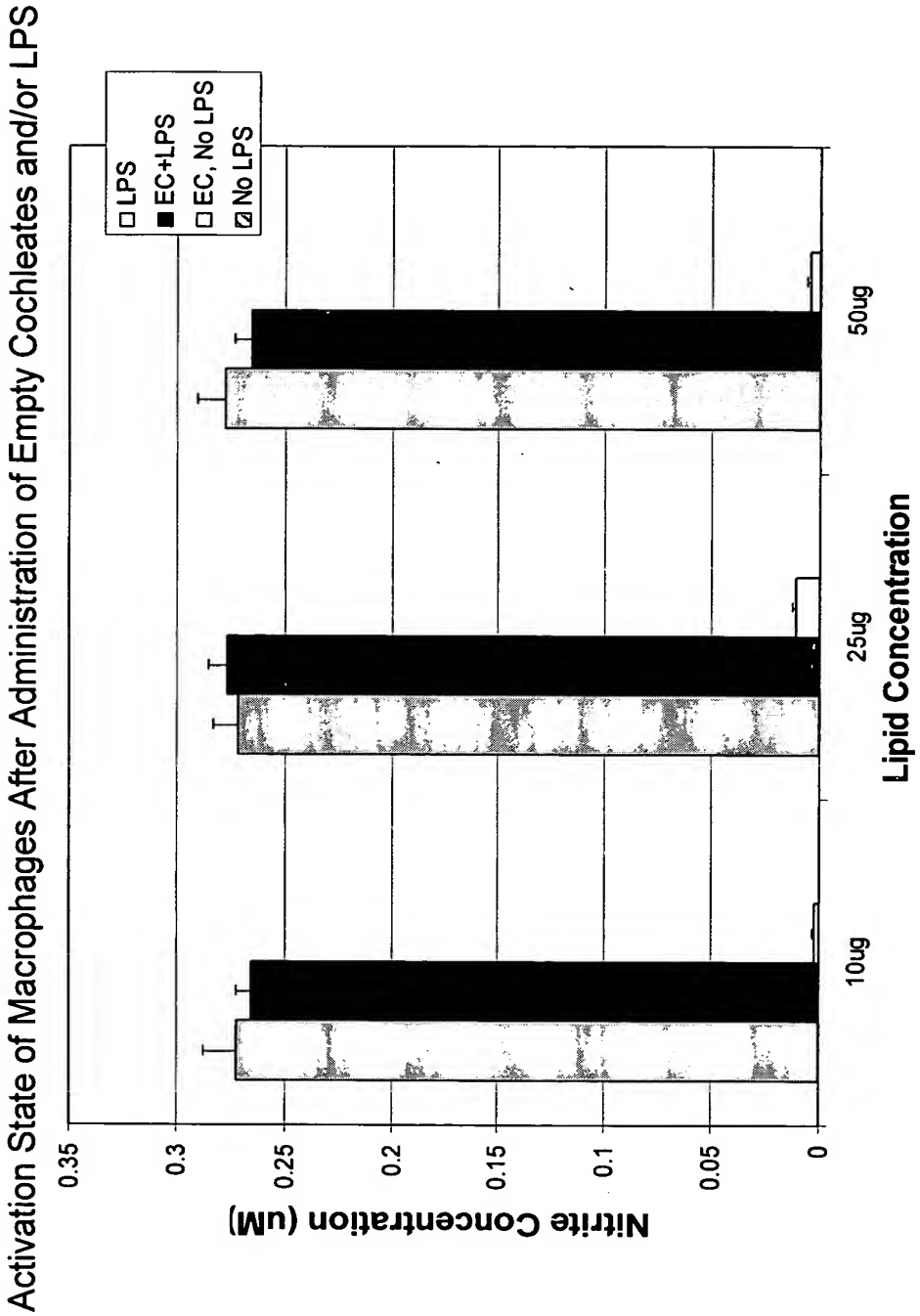
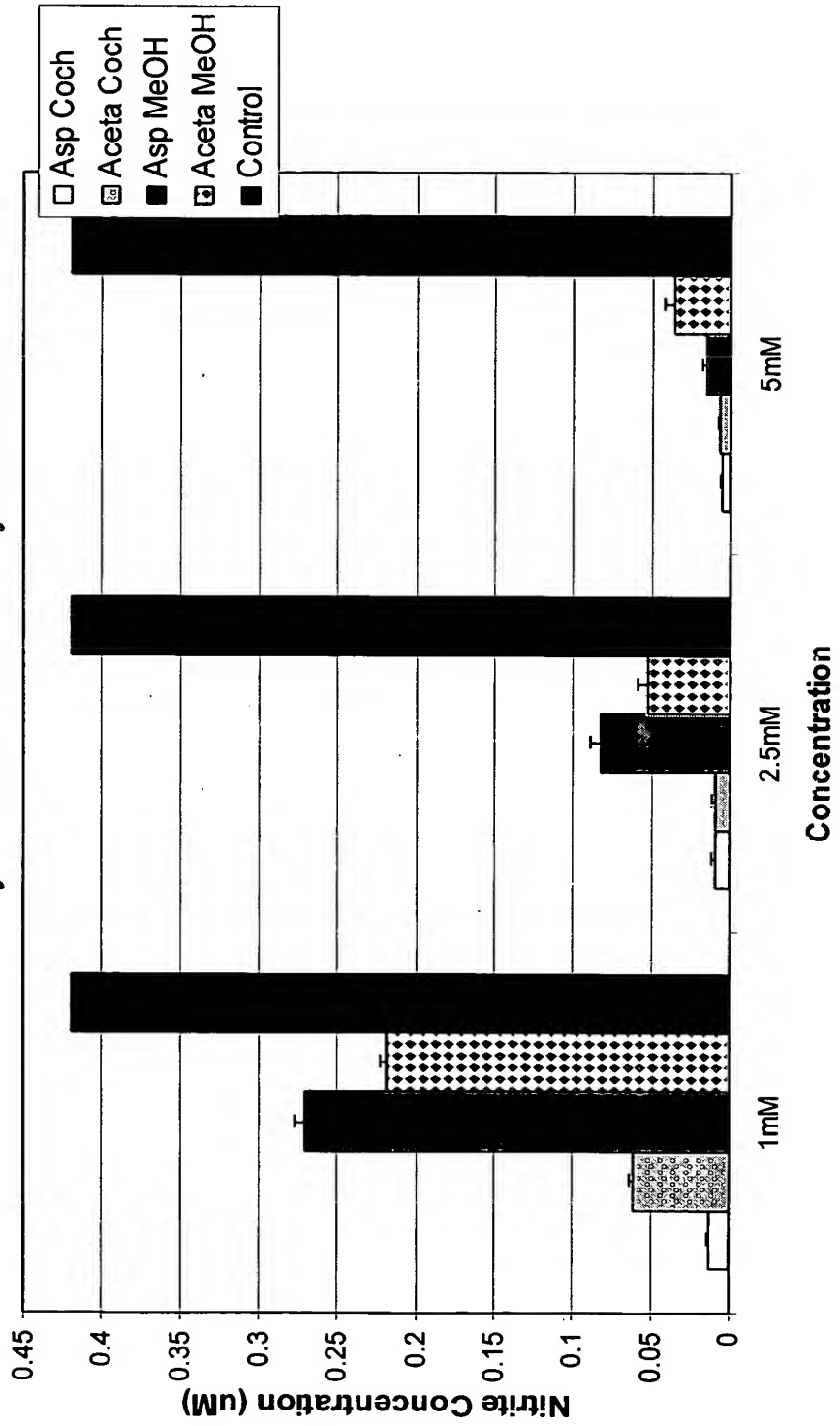

Activation State of Macrophages After Administration of Empty Cochleates and/or LPS
LPS
EC+LPS
EC, No LPS
No LPS
Nitrite Concentration (uM)
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
10ug
25ug
50ug
Lipid Concentration

Figure 41

In Vitro Efficacy of Anti-Inflammatory Cochleates



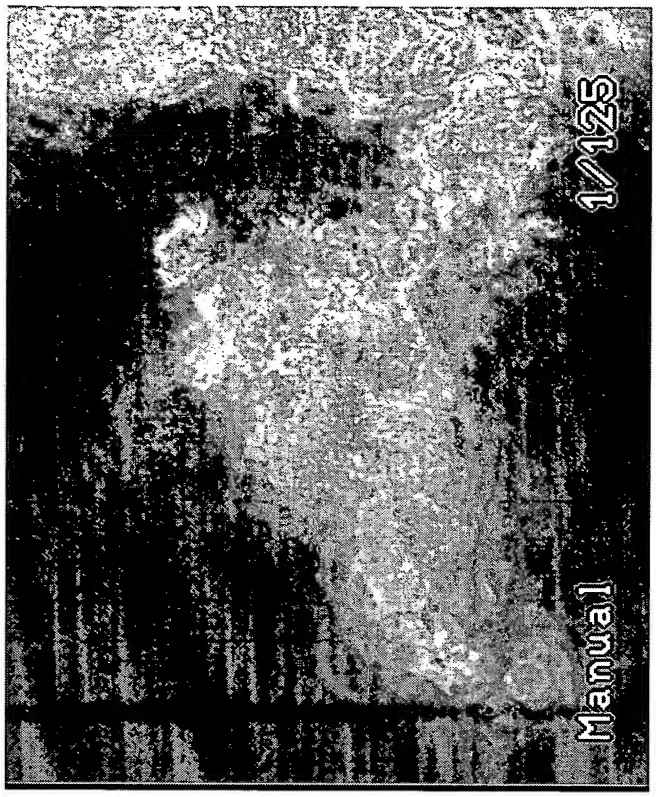


Figure 43

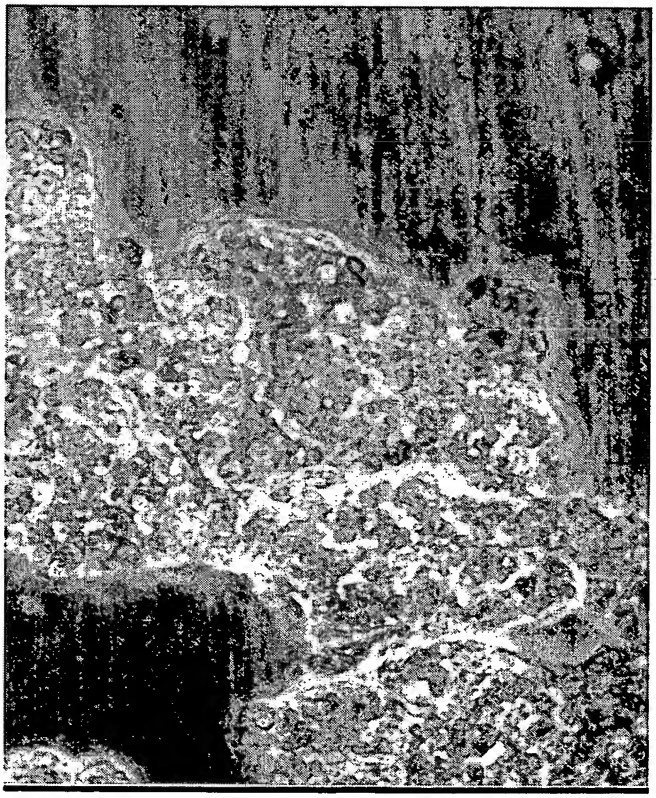


Figure 42

Figure 44

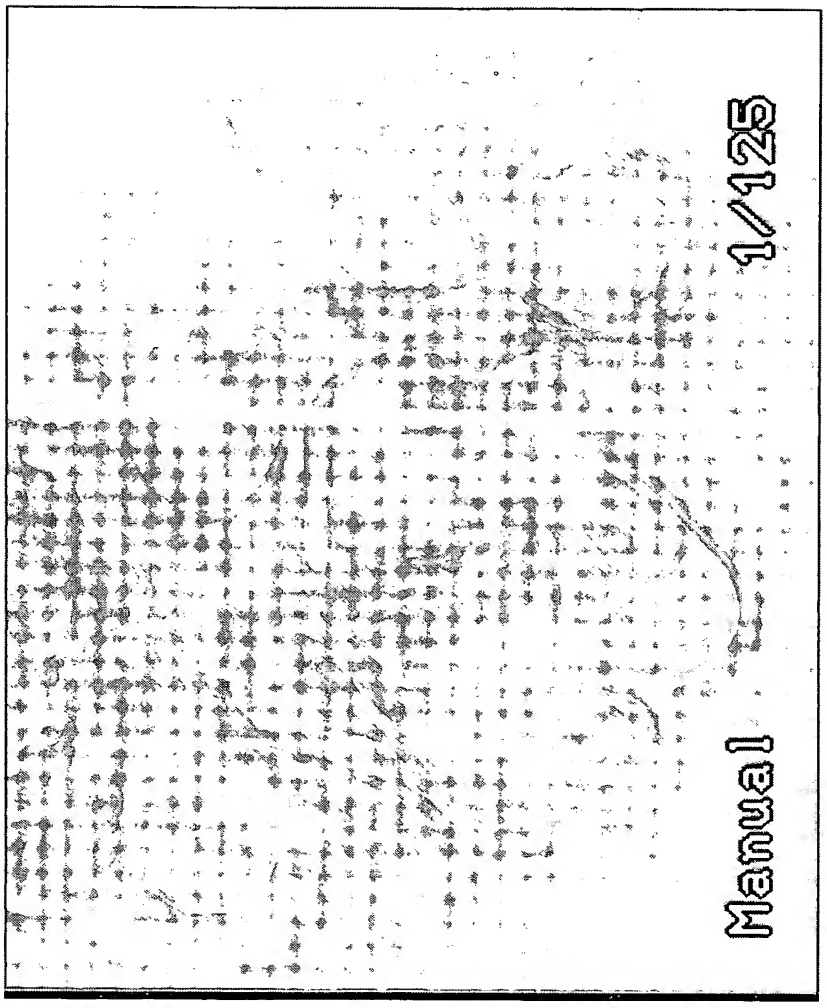
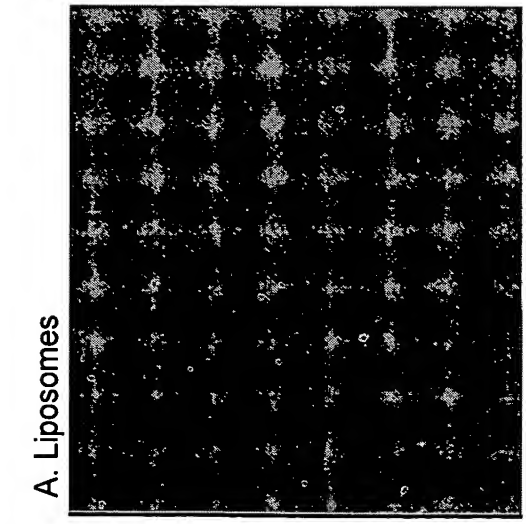
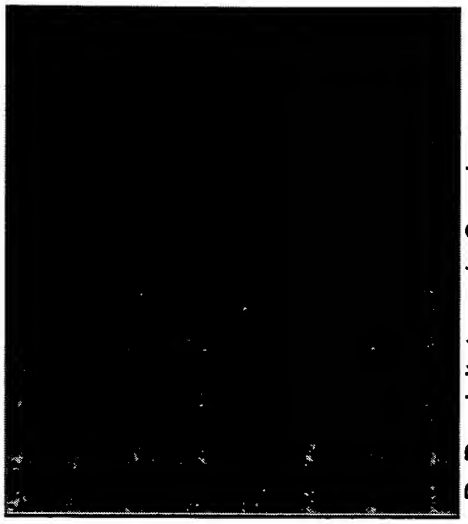
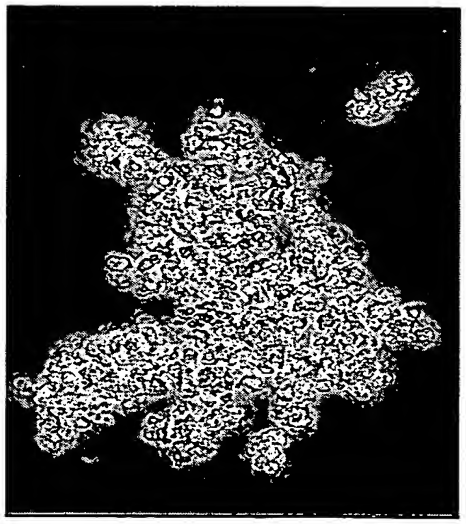


Figure 45
Vancomycin


A. Liposomes


B. Precipitates with casein


C. Precipitates without Casein

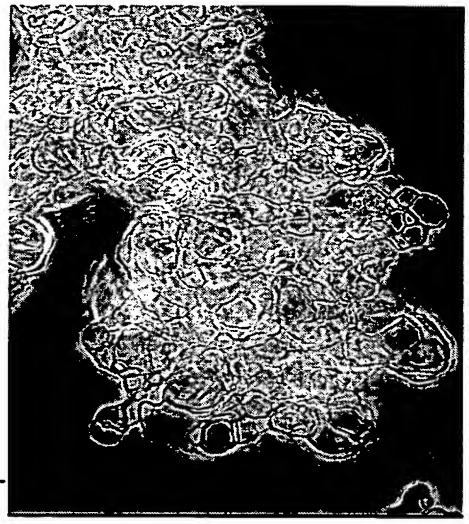
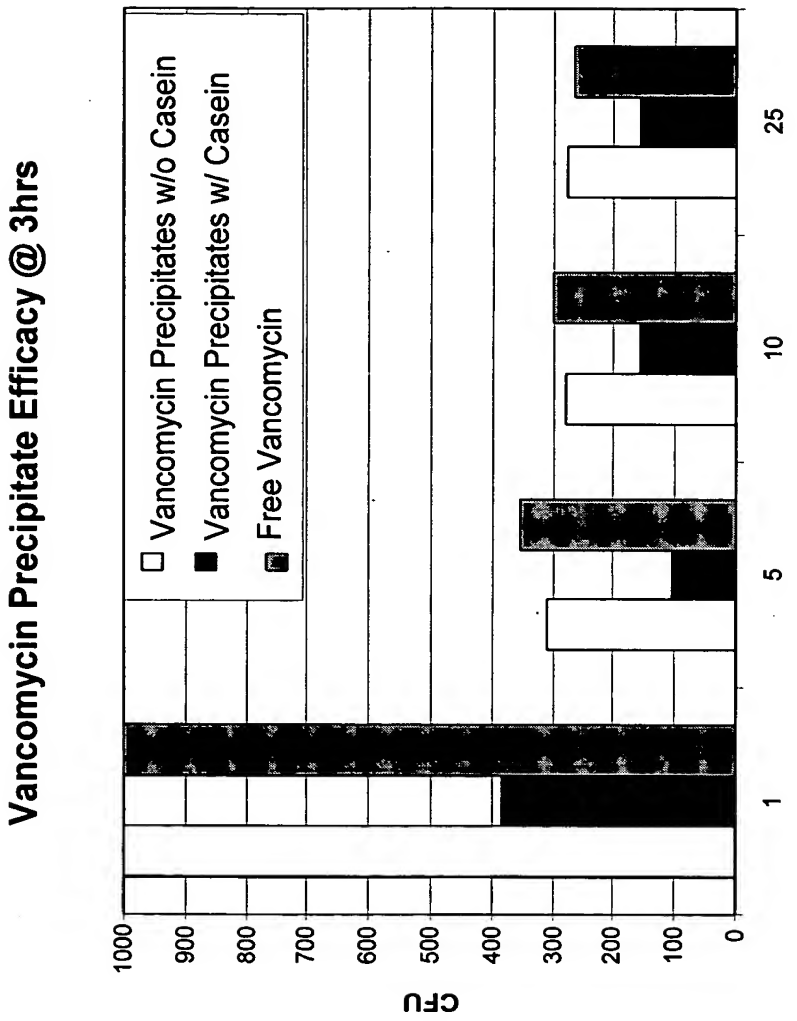
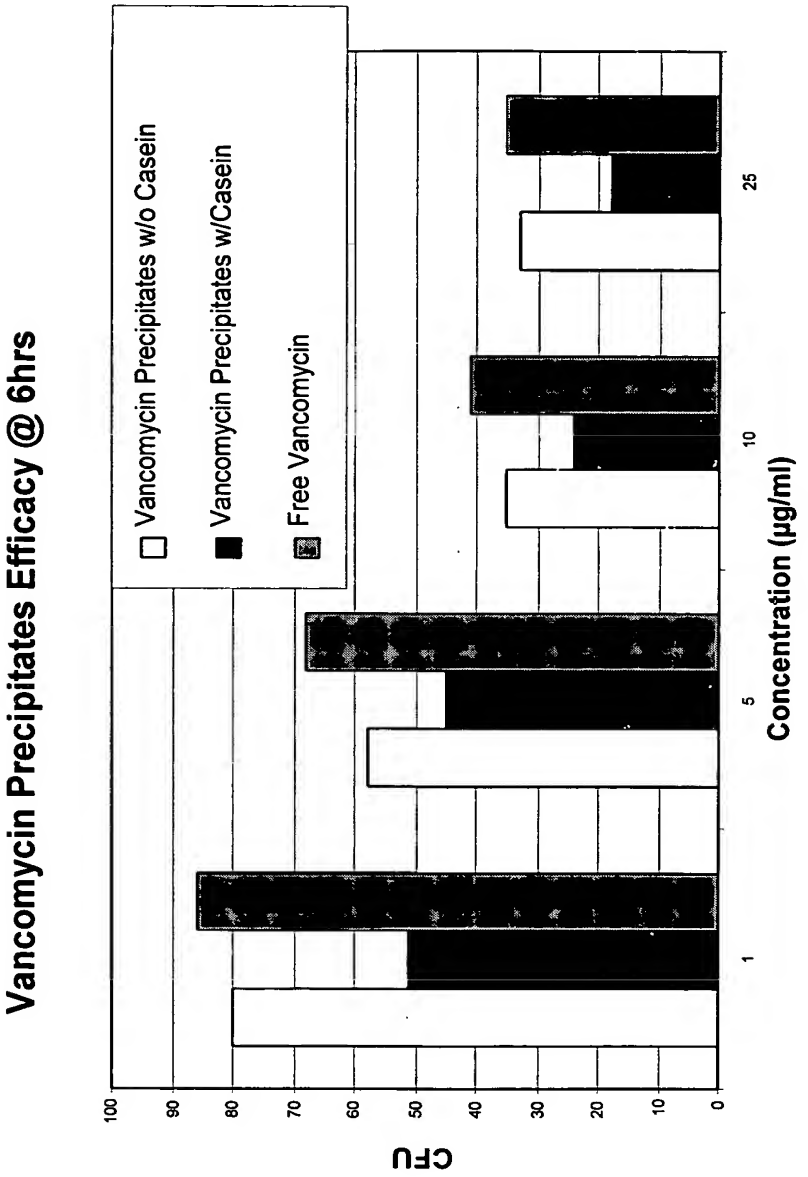

D. Precipitates w/o Casein upon addition of EDTA

Figure 46



***In Vitro* Efficacy of Vancomycin Precipitates in Macrophages Infected with *Staphylococcal aureus* at 3 hours post infection.**

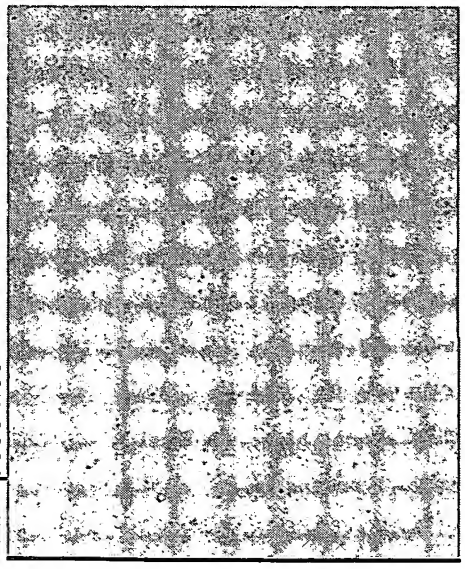
Figure 47

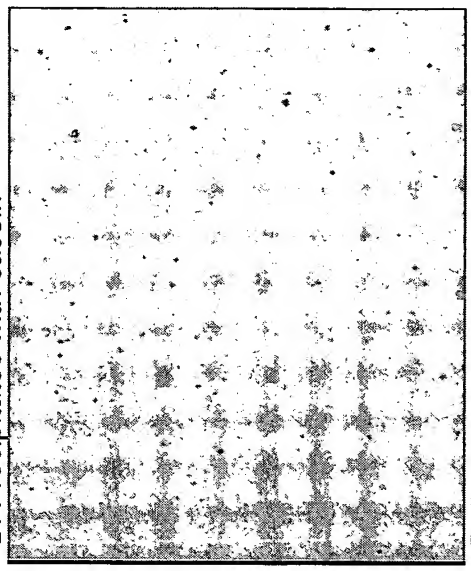


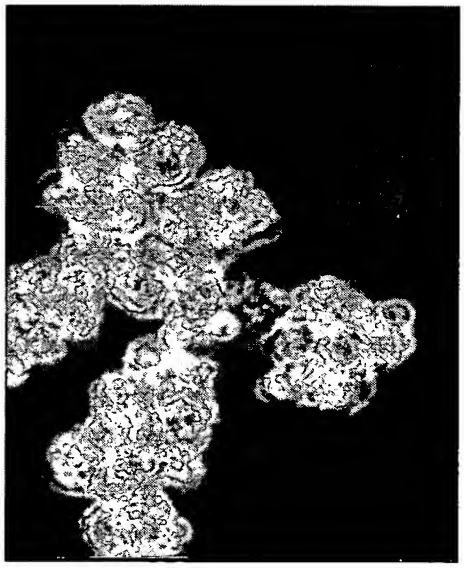
***In Vitro* Efficacy of Vancomycin Precipitates in Macrophages Infected with *Staphylococcal aureus* at 6 hours post infection.**

Figure 48

Tobramycin







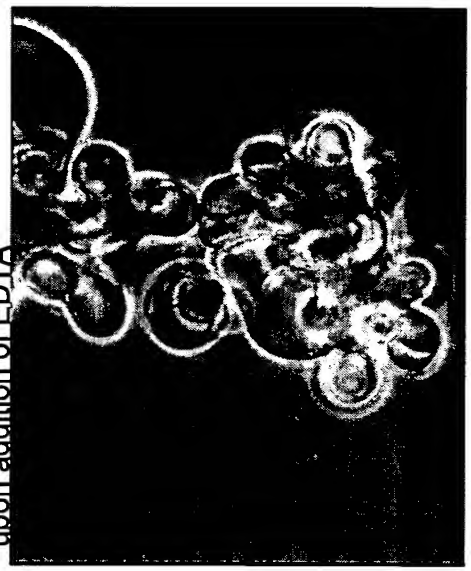


Figure 49

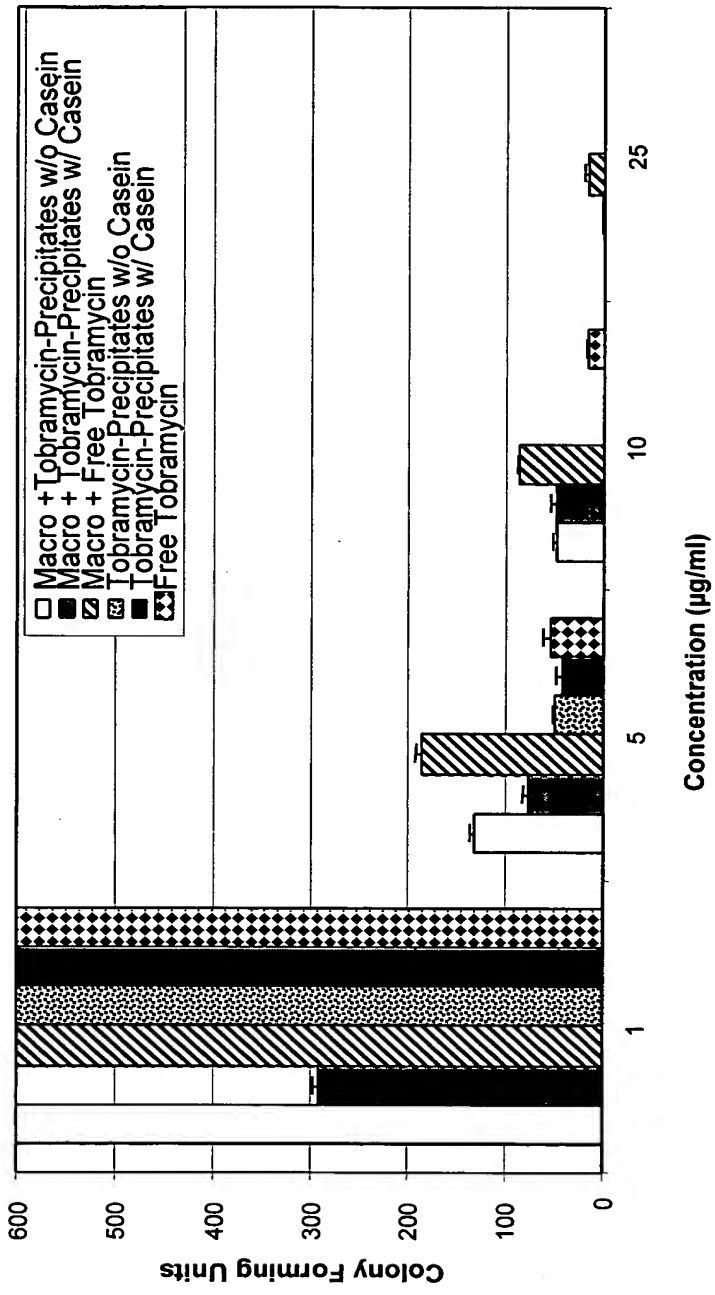

Efficacy of Tobramycin Formulations Against
Pseudomonas aeruginosa at 3 Hours Post-Infection
Macro +Tobramycin-Precipitates w/o Casein
Macro + Tobramycin-Precipitates w/ Casein
Macro + Free Tobramycin
Tobramycin-Precipitates w/o Casein
Tobramycin-Precipitates w/ Casein
Free Tobramycin
Colony Forming Units
0
100
200
300
400
500
600
1
5
10
25
Concentration (µg/ml)

Figure 50

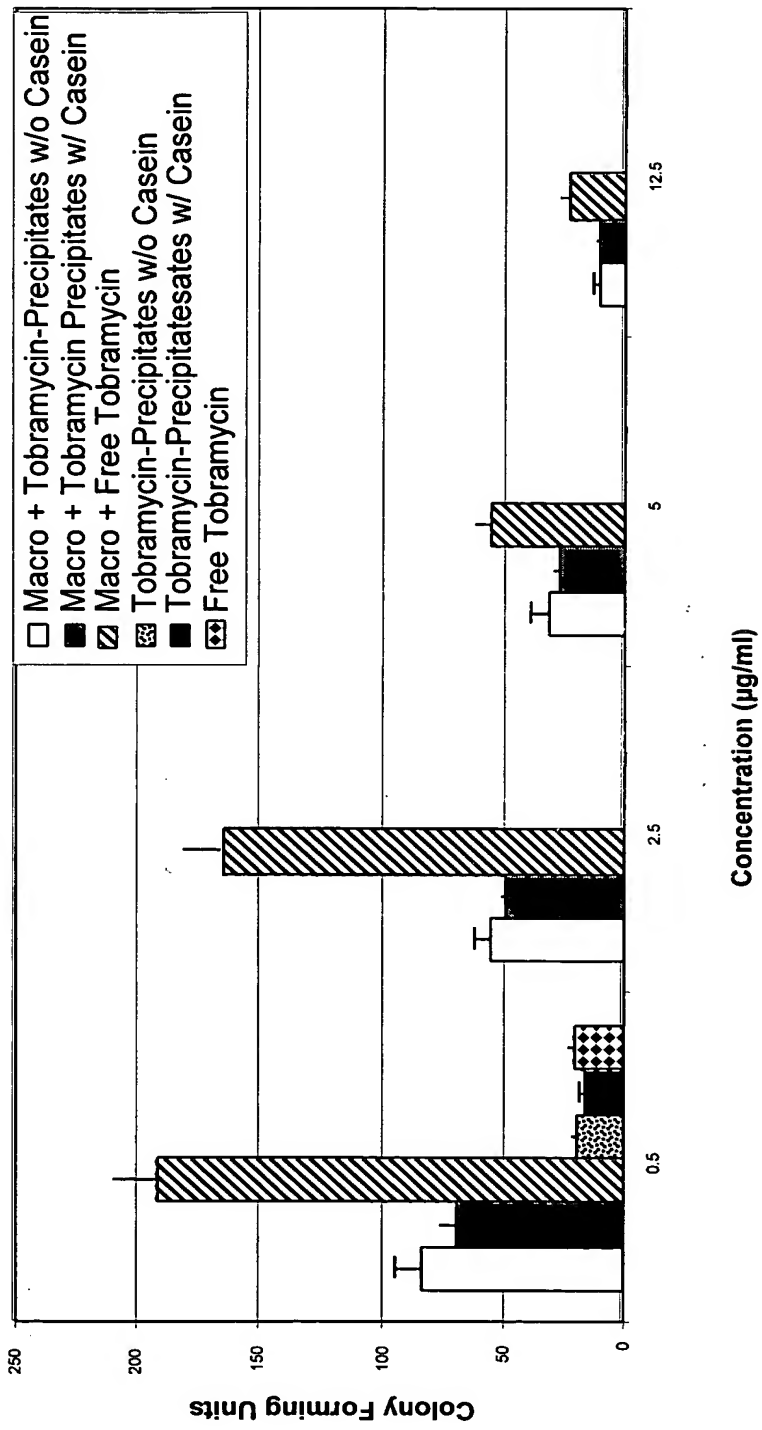

Efficacy of Tobramycin Formulations Against
Pseudomonas aeruginosa at 6 Hours Post-Infection
Macro + Tobramycin-Precipitates w/o Casein
Macro + Tobramycin Precipitates w/ Casein
Macro + Free Tobramycin
Tobramycin-Precipitates w/o Casein
Tobramycin-Precipitatesates w/ Casein
Free Tobramycin
Colony Forming Units
250
200
150
100
50
0
0.5
2.5
5
12.5
Concentration (µg/ml)

Figure 51

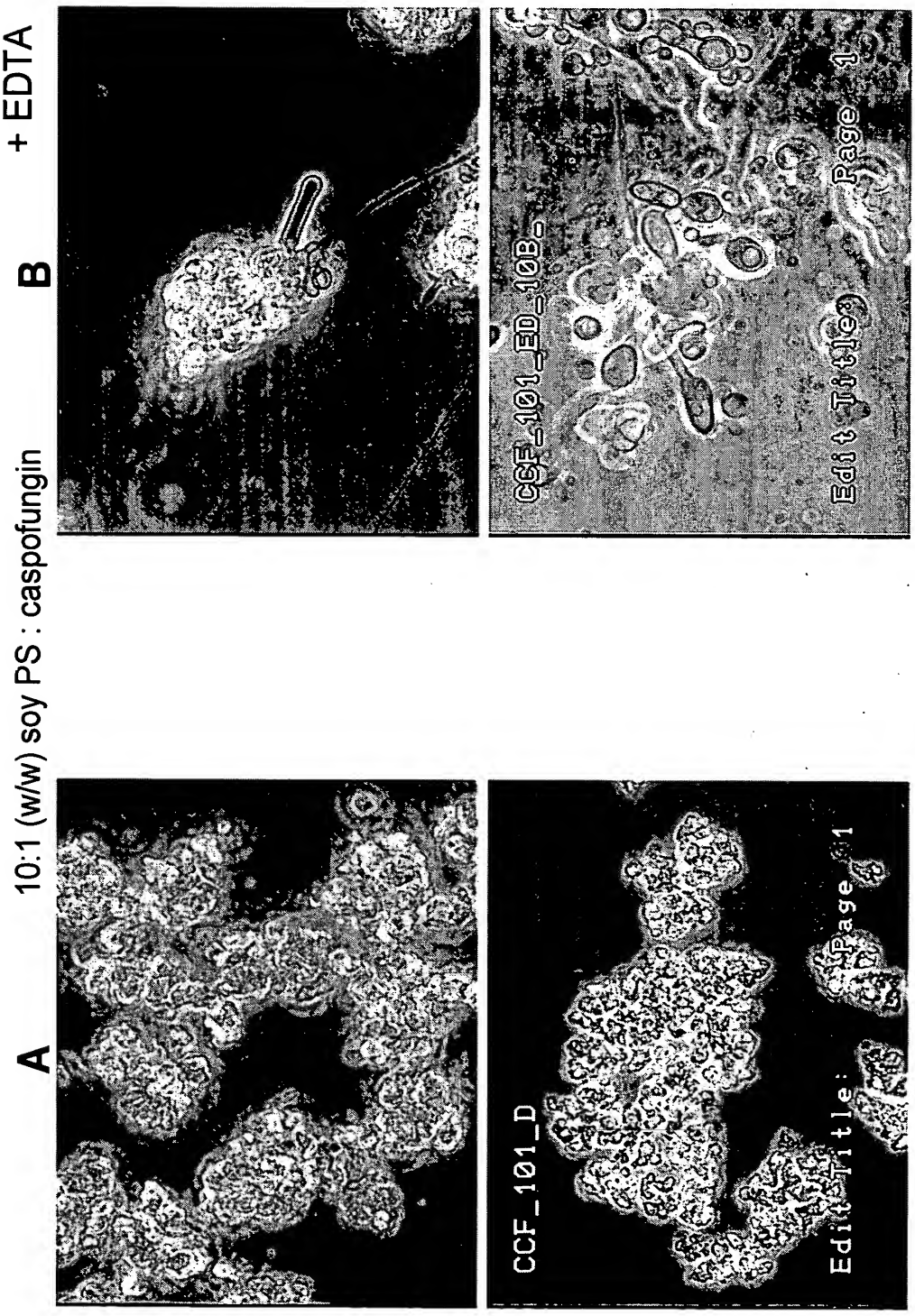

A
10:1 (w/w) soy PS : caspofungin
B
+ EDTA
CCF_101_D
Edit Title
Page 1
CCF_101_ED_10B_
Edit Title
Page 1

Figure 52

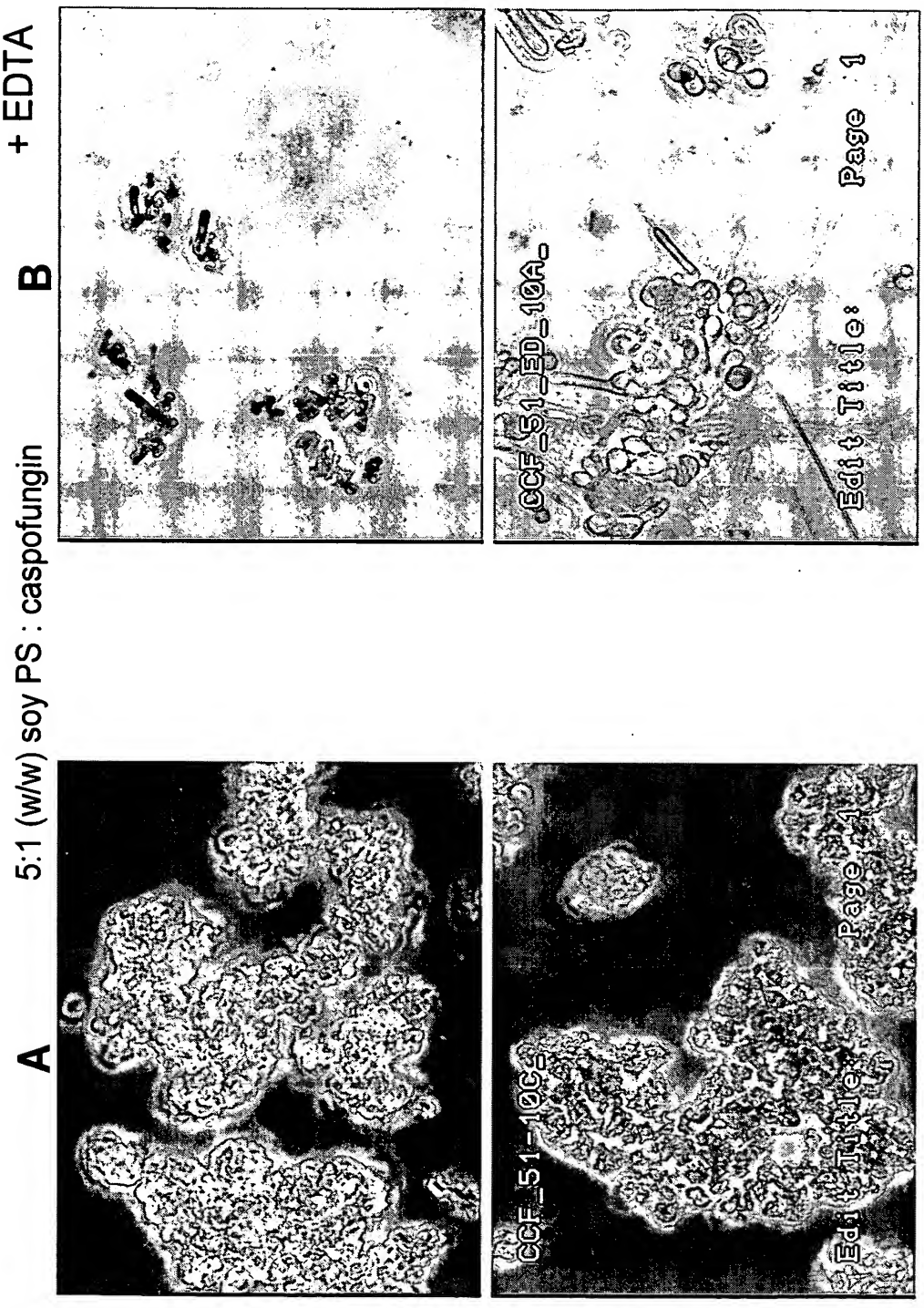

A
5:1 (w/w) soy PS : caspofungin
B
+ EDTA
CCF_51_10C1
Edit Title: Page 1
CCF_51_ED_10A_
Edit Title: Page 1

Figure 53

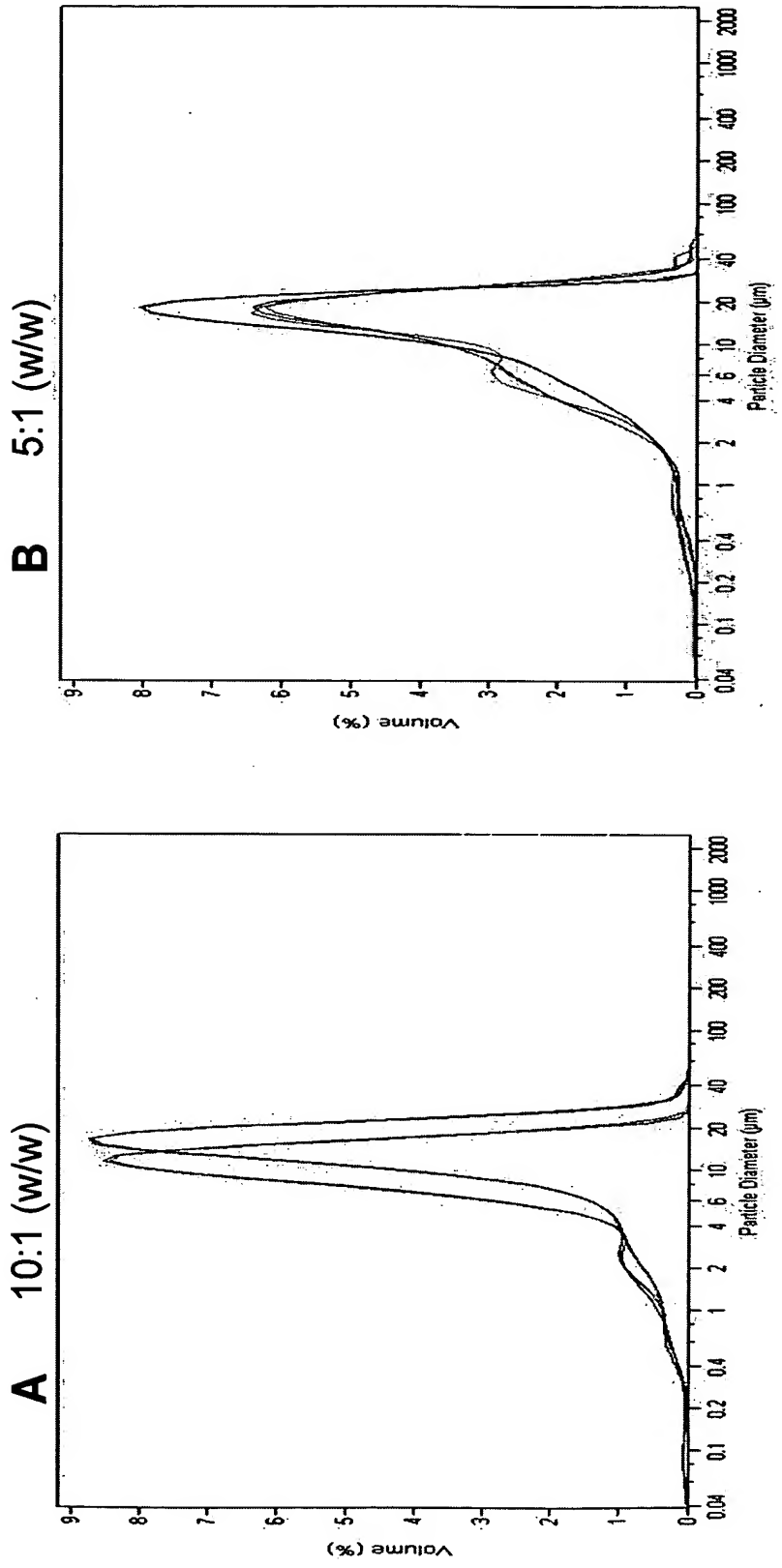

A
10:1 (w/w)
B
5:1 (w/w)
Volume (%)
Particle Diameter (µm)
0.04
0.1
0.2
0.4
1
2
4
6
10
20
40
100
200
400
1000
2000
0
1
2
3
4
5
6
7
8
9

Figure 54

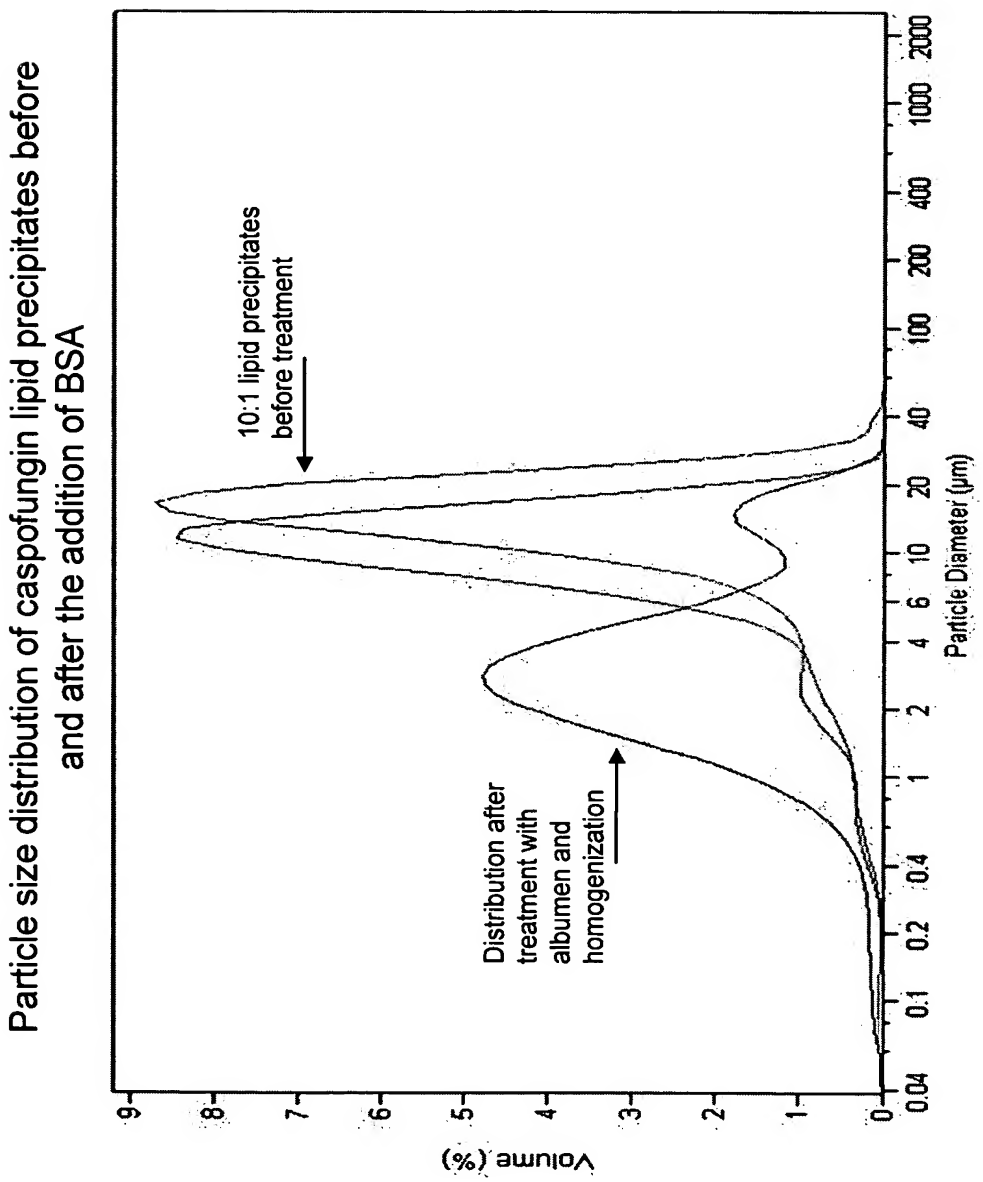

Particle size distribution of caspofungin lipid precipitates before and after the addition of BSA
10:1 lipid precipitates before treatment
Distribution after treatment with albumen and homogenization
Volume (%)
Particle Diameter (µm)
0
1
2
3
4
5
6
7
8
9
0.04
0.1
0.2
0.4
1
2
4
6
10
20
40
100
200
400
1000
2000

Figure 55

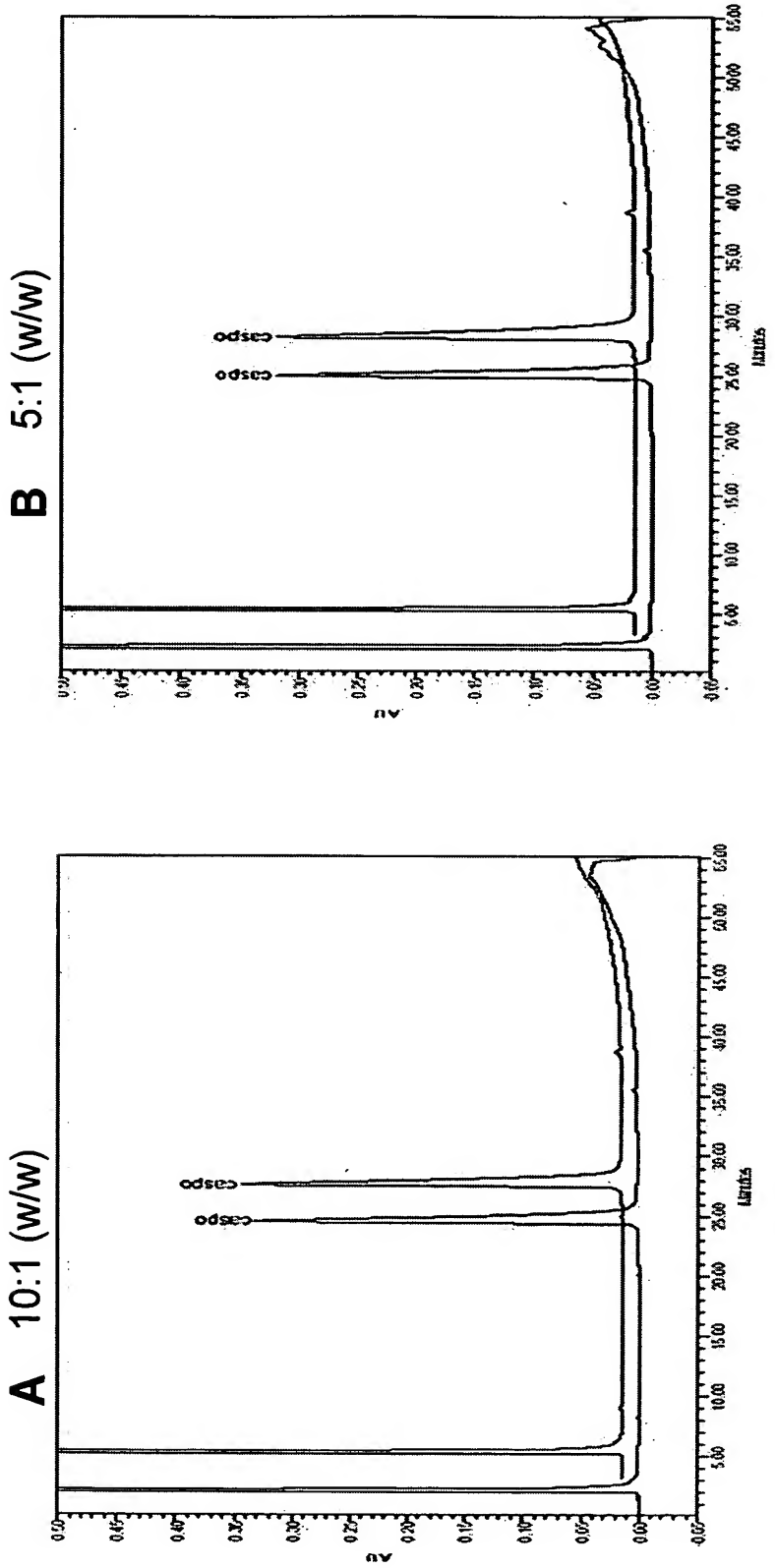


Figure 56

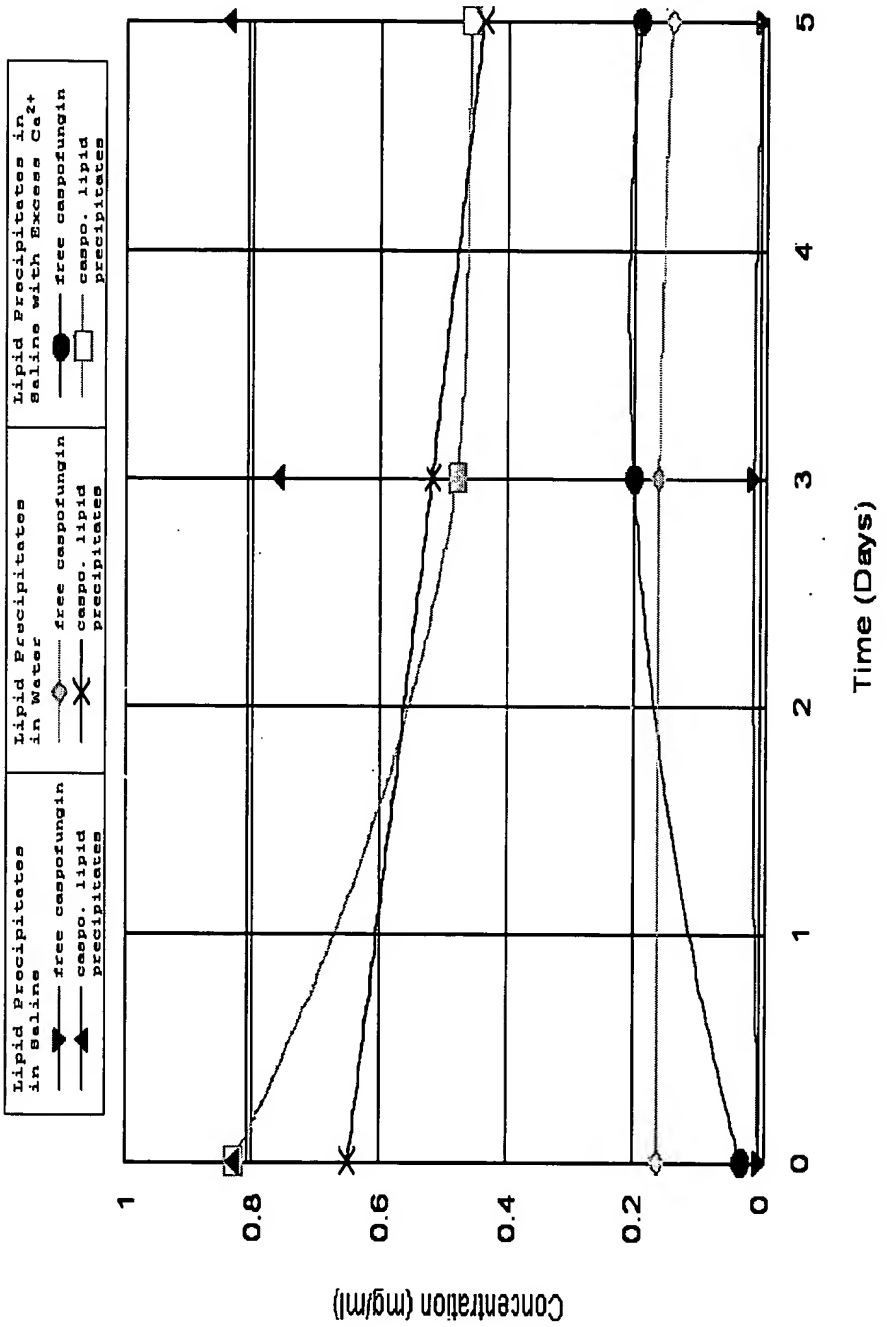

Lipid Precipitates in Saline
free caspofungin
caspo. lipid precipitates
Lipid Precipitates in Water
free caspofungin
caspo. lipid precipitates
Lipid Precipitates in Saline with Excess Ca2+
free caspofungin
caspo. lipid precipitates
Concentration (mg/ml)
1
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
Time (Days)

Figure 57

Structure of caspofungin lipid precipitates as a function of pH.

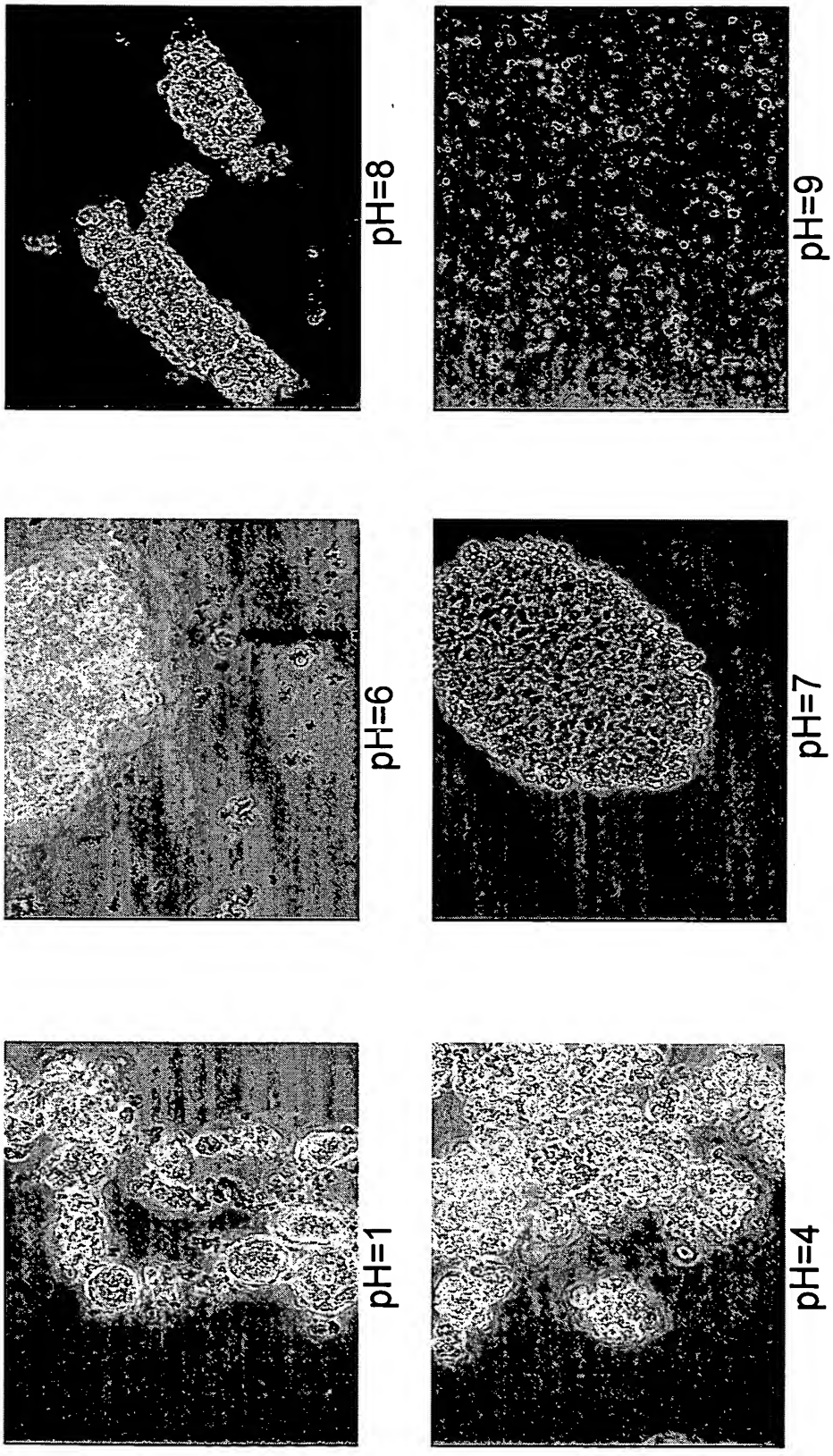


Figure 58

AmB Cochleates Containing 0.2% (w/w) Parabens

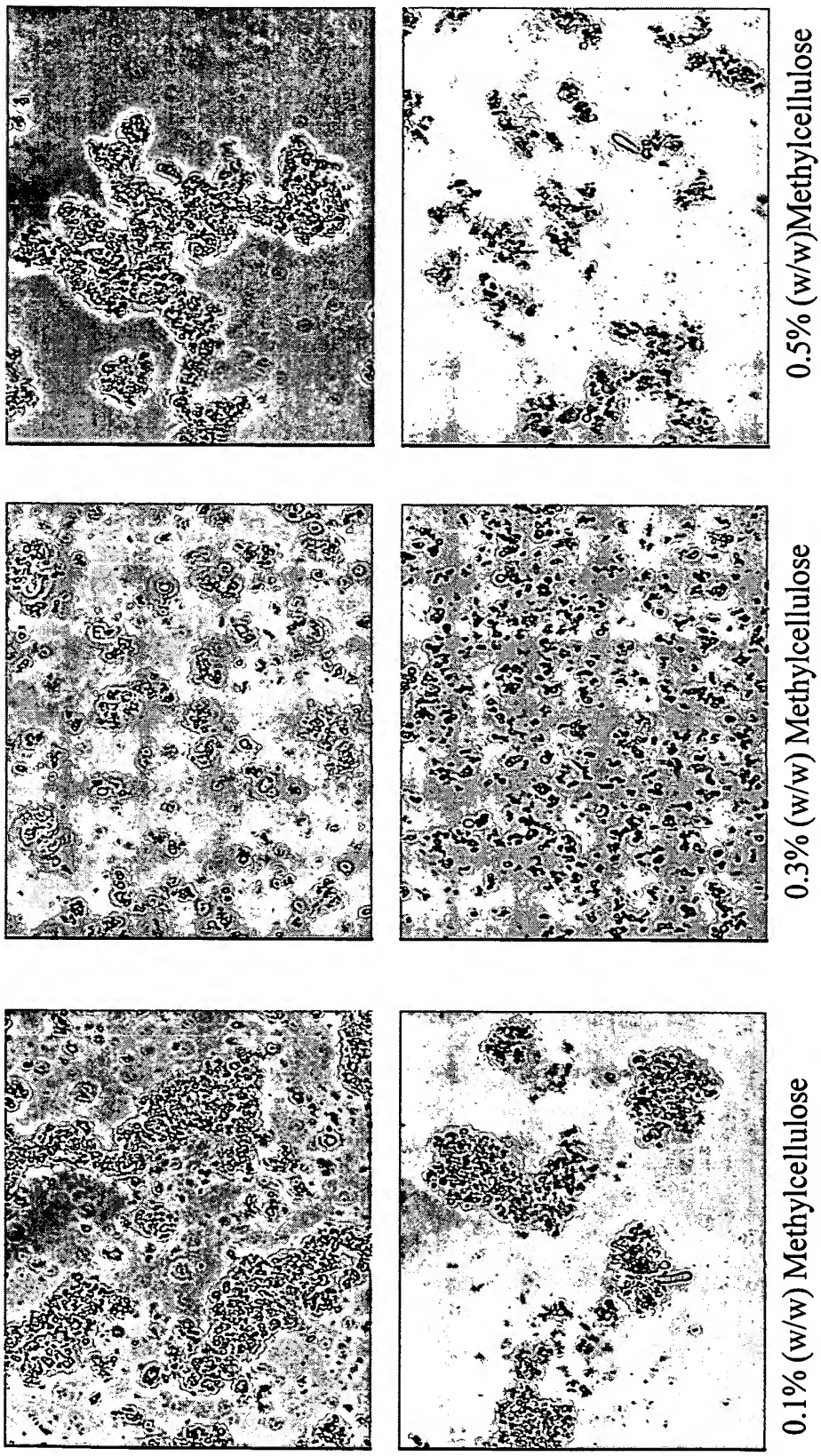


Figure 59

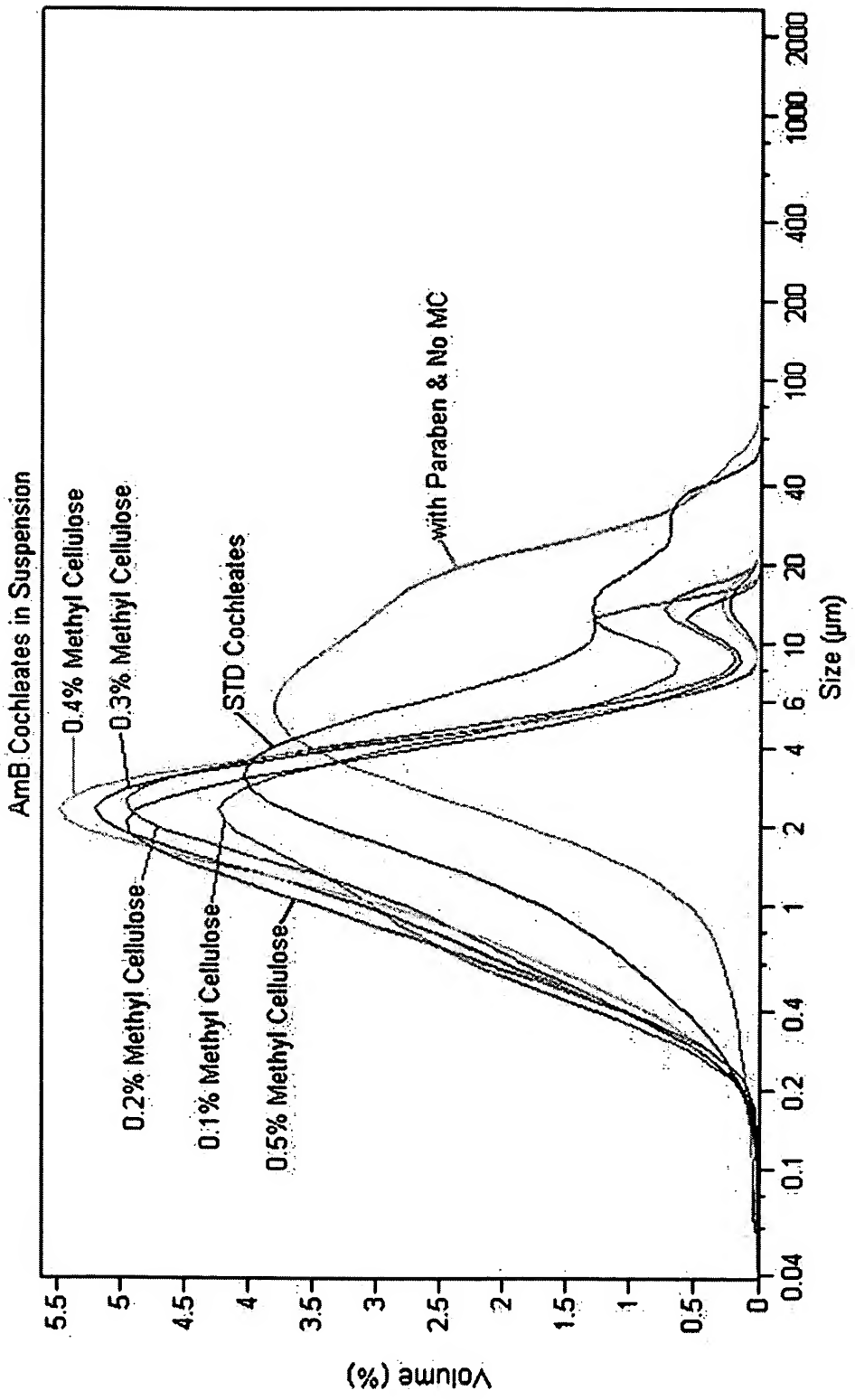

AmB Cochleates in Suspension
0.4% Methyl Cellulose
0.3% Methyl Cellulose
STD Cochleates
with Paraben & No MC
0.2% Methyl Cellulose
0.1% Methyl Cellulose
0.5% Methyl Cellulose
Volume (%)
Size (µm)
0.04
0.1
0.2
0.4
1
2
4
6
10
20
40
100
200
400
1000
2000
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5

Figure 60

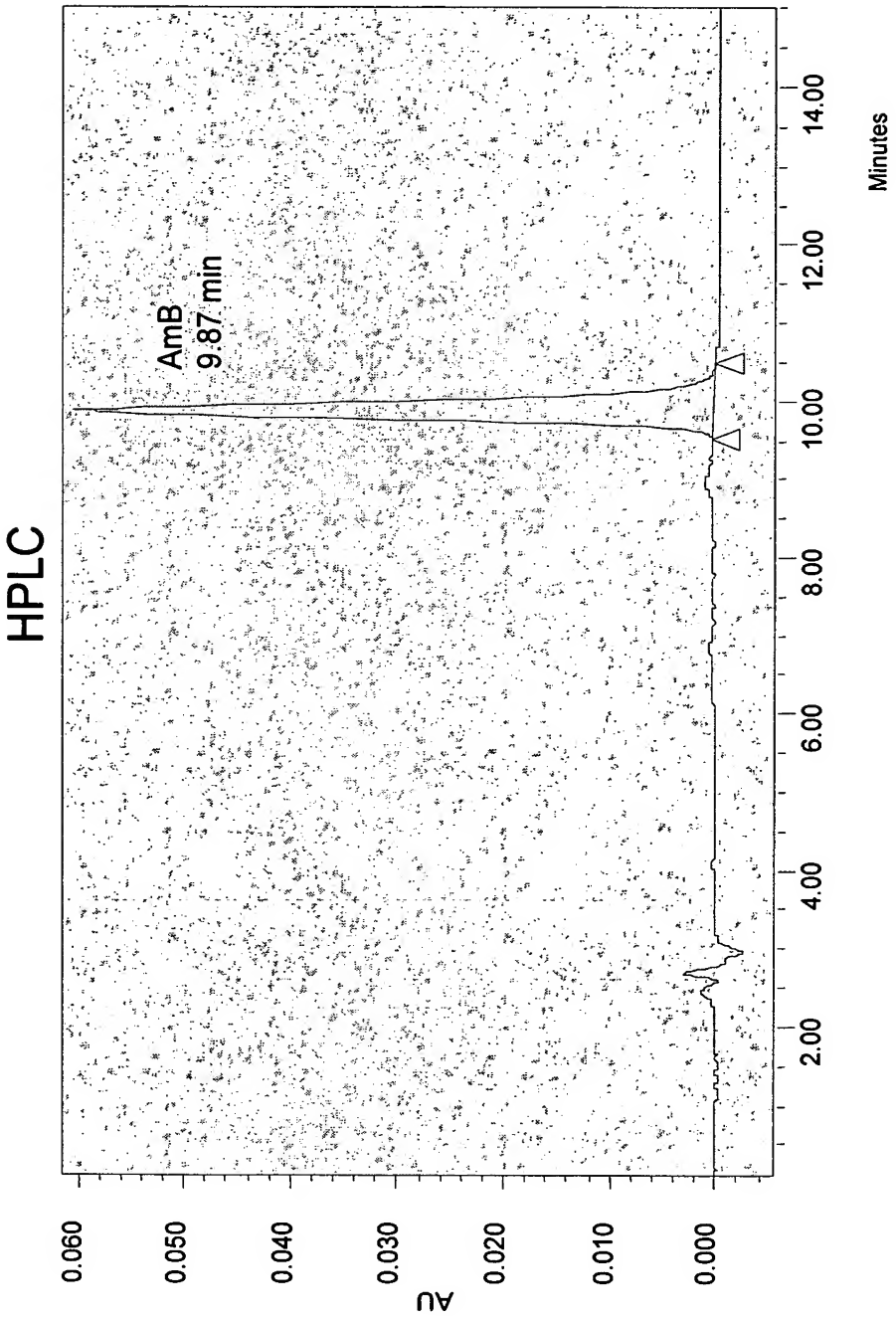

HPLC
AmB
9.87 min
AU
0.060
0.050
0.040
0.030
0.020
0.010
0.000
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes

Figure 61

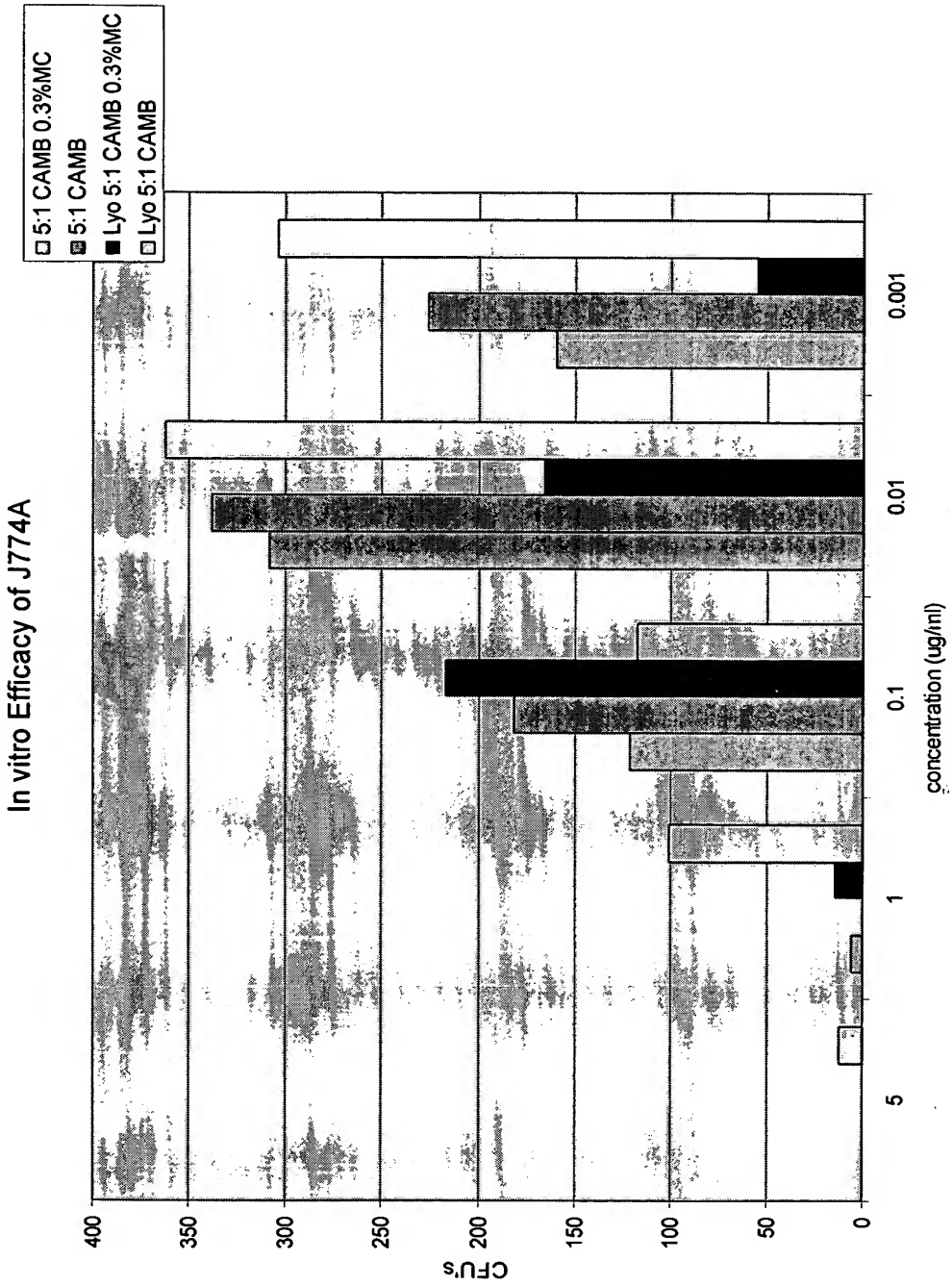

In vitro Efficacy of J774A
5:1 CAMB 0.3%MC
5:1 CAMB
Lyo 5:1 CAMB 0.3%MC
Lyo 5:1 CAMB
CFUs
400
350
300
250
200
150
100
50
0
5
1
0.1
0.01
0.001
concentration (ug/ml)

Figure 62

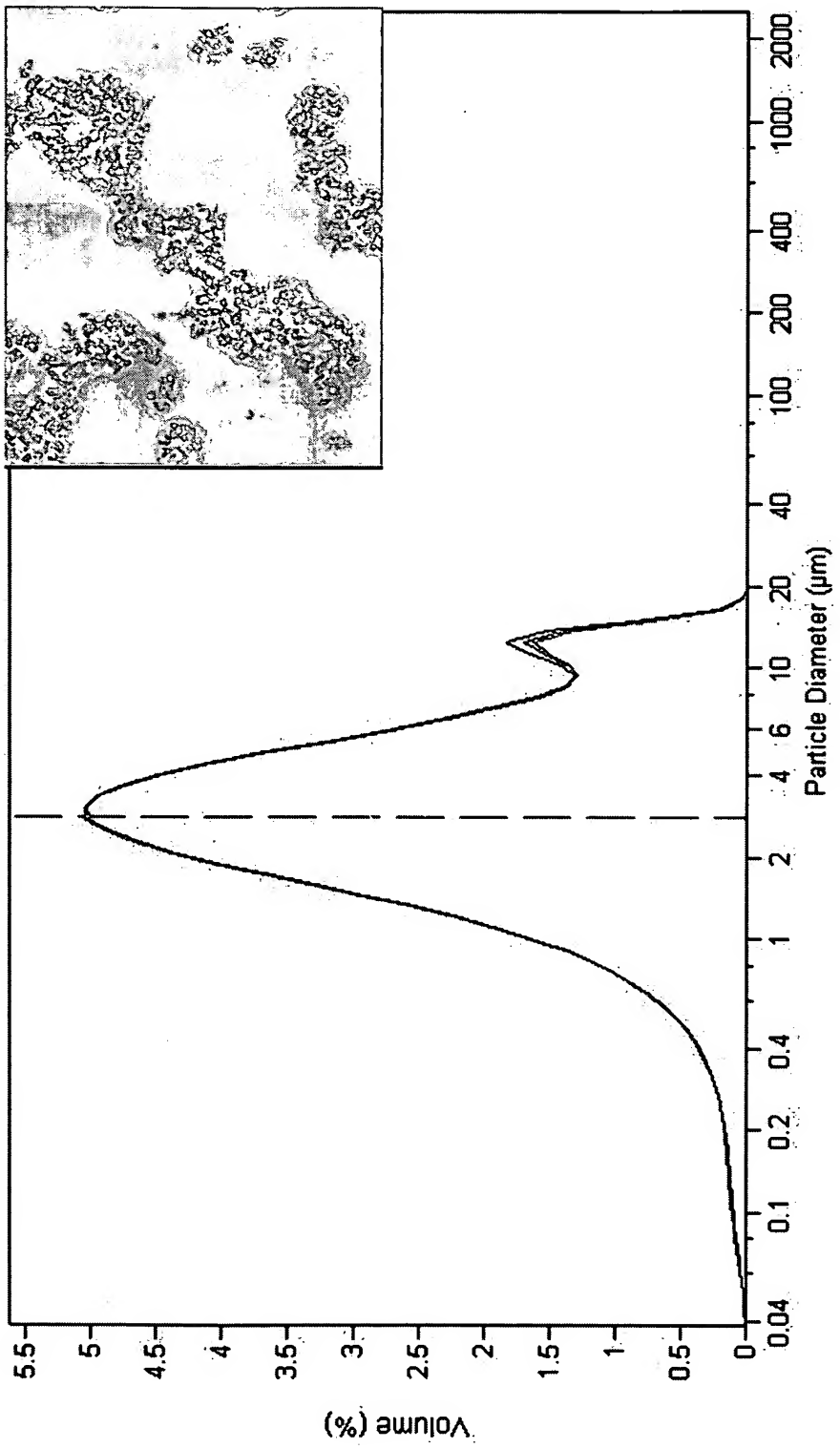

Volume (%)
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0.04
0.1
0.2
0.4
1
2
4
6
10
20
40
100
200
400
1000
2000
Particle Diameter (µm)

Figure 63

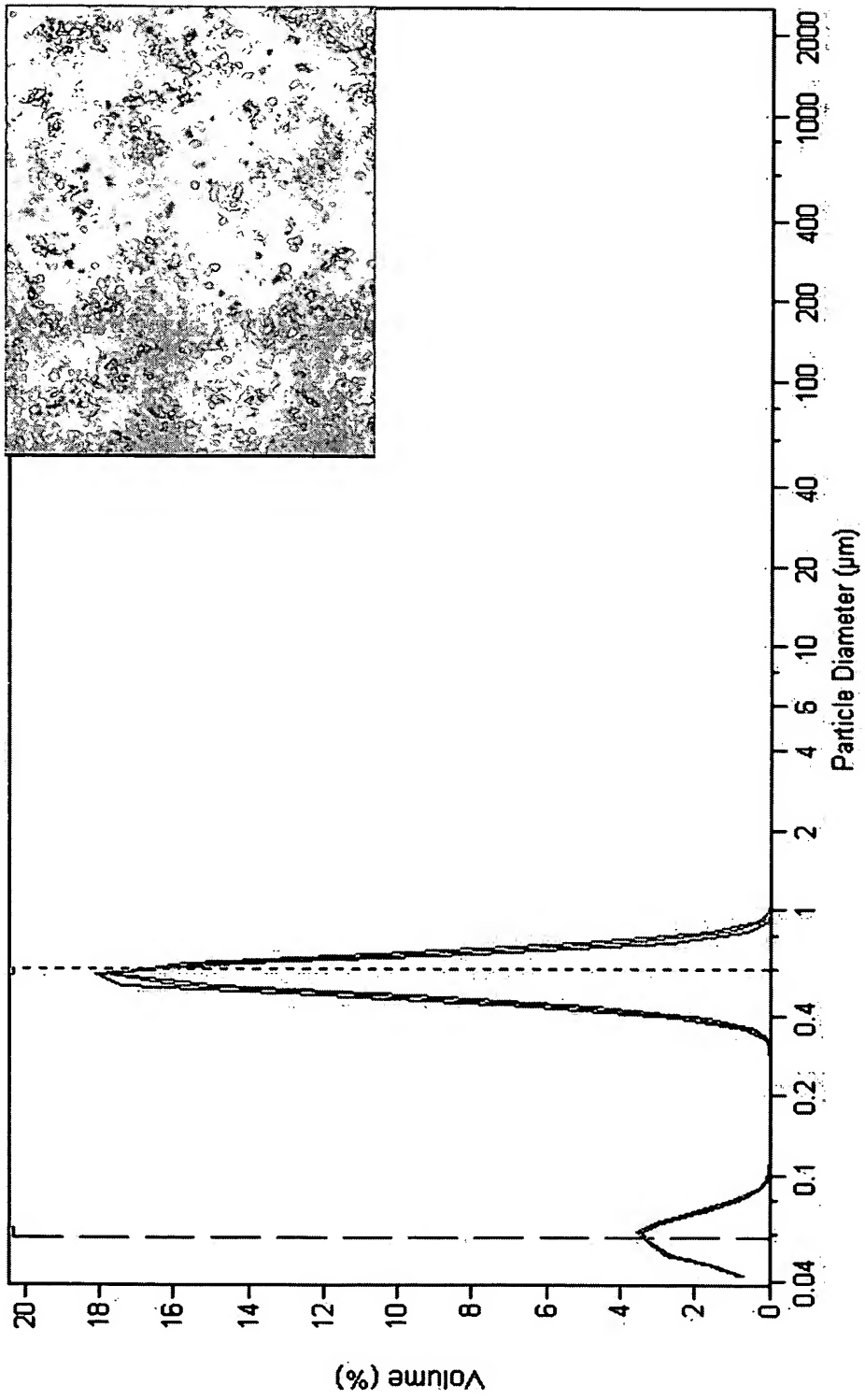
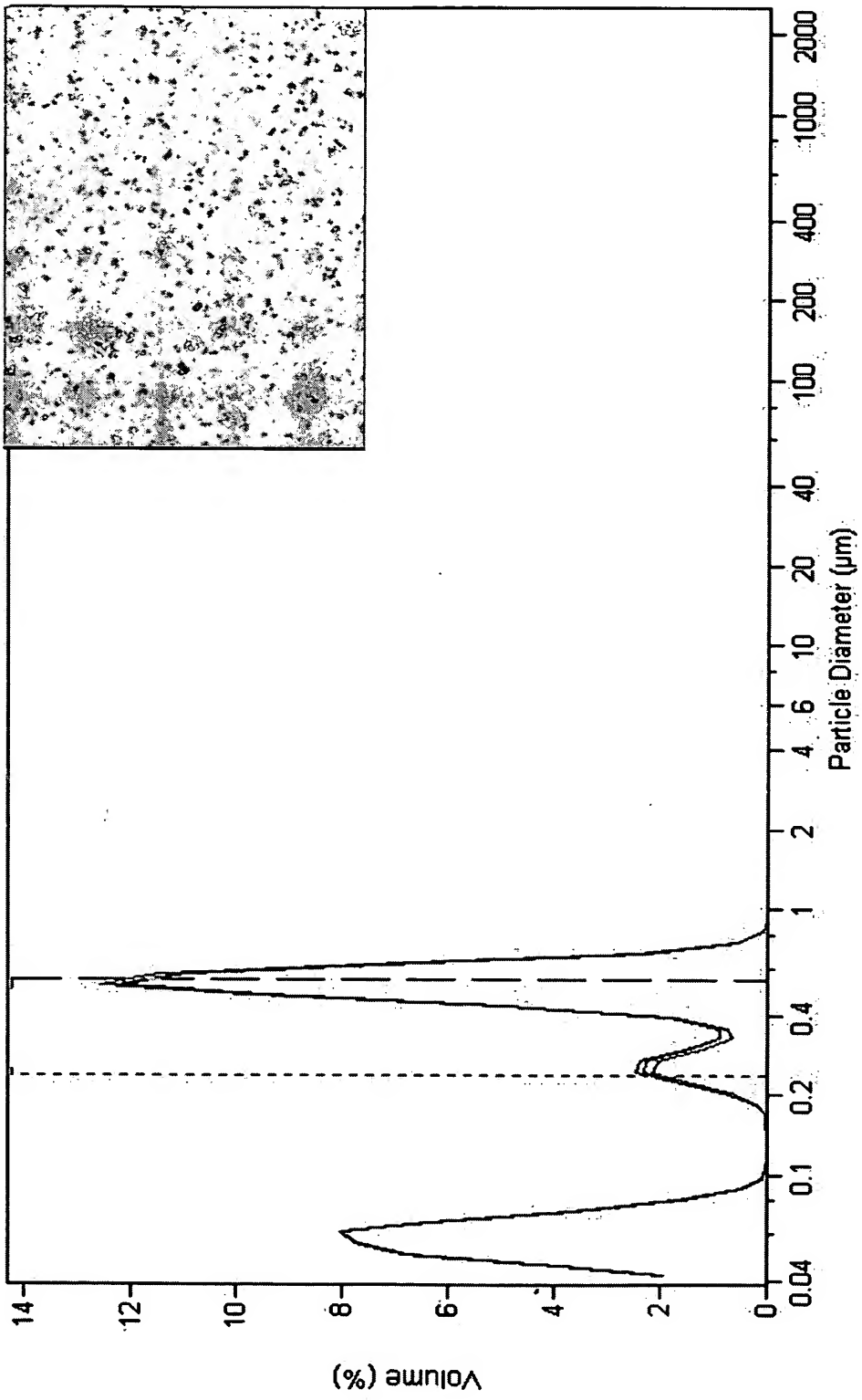

Volume (%)
0
2
4
6
8
10
12
14
16
18
20
0.04
0.1
0.2
0.4
1
2
4
6
10
20
40
100
200
400
1000
2000
Particle Diameter (µm)

Figure 64


Volume (%)
0
2
4
6
8
10
12
14
0.04
0.1
0.2
0.4
1
2
4
6
10
20
40
100
200
400
1000
2000
Particle Diameter (µm)